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British Journal of Anaesthesia

Editor of General Issues
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Editor of Postgraduate Educational Issues
J. NORMAN
M.B., CH.B., PH.D., F.F.A.R.C.S.

VOLUME 52
1980

Published by
MACMILLAN PUBLISHERS LTD
4 Little Essex Street
LONDON WC2R 3LF

© Macmillan Publishers Ltd, 1980

Printed in Great Britain by John Wright and Sons Ltd
The Stonebridge Press, Bath Road, Bristol BS4 5NU

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The GUIDE TO CONTRIBUTORS can be found on pages x, xii & xiv of the advertisement section of this issue.

Published monthly. Annual subscriptions: U.K. £22·50, U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27·50, Airmail £50; (or equivalent in any other currency). ISSN 0007–0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.

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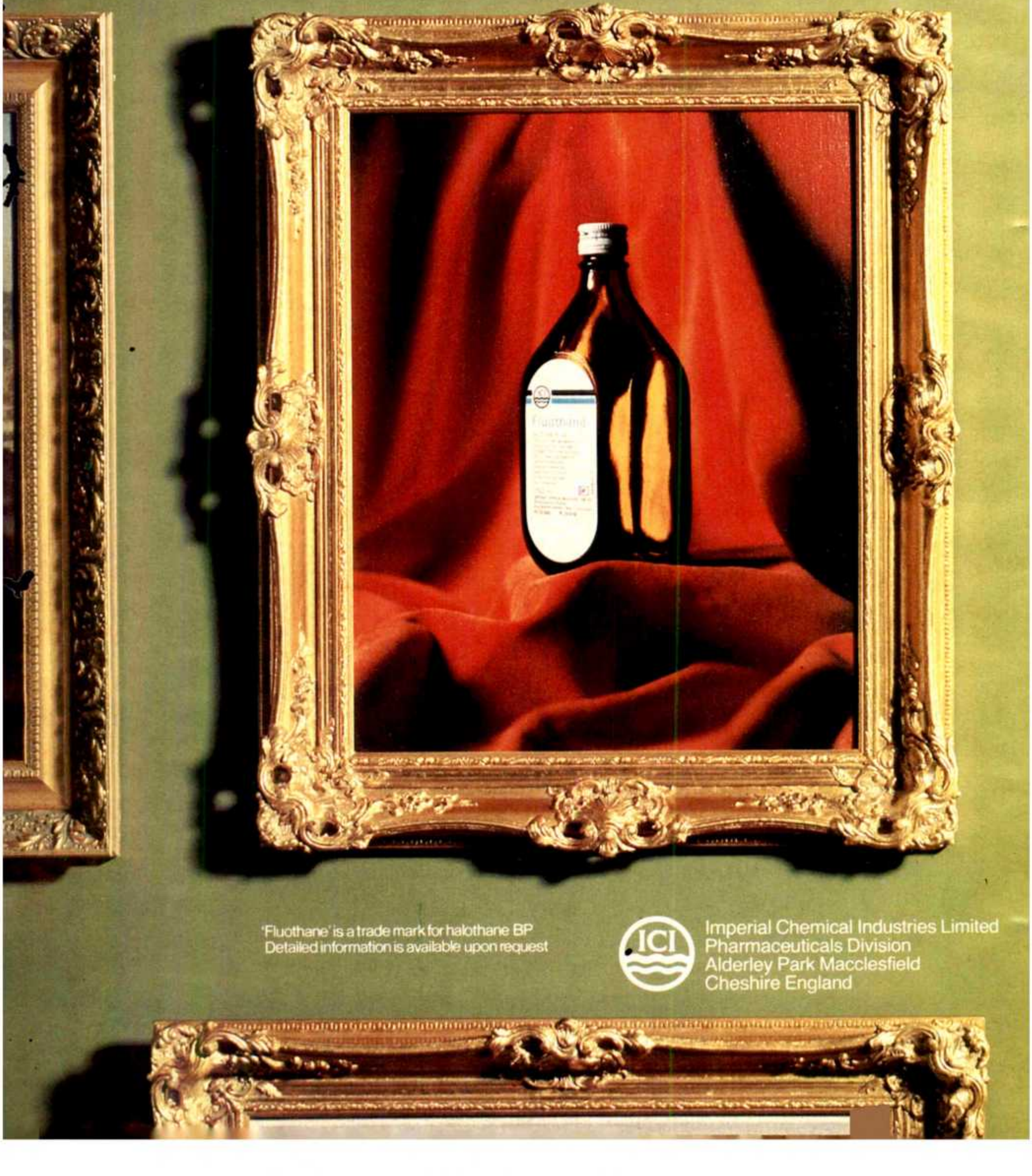

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passive system: 230–300 ppm N_2O
Howorth system: 0–3 ppm N_2O
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1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

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Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, and of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post-operative nausea and vomiting are infreque There have been occasional reports of more severe reactions. Bronchospasm and/or a marke drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids an plasma expanders.

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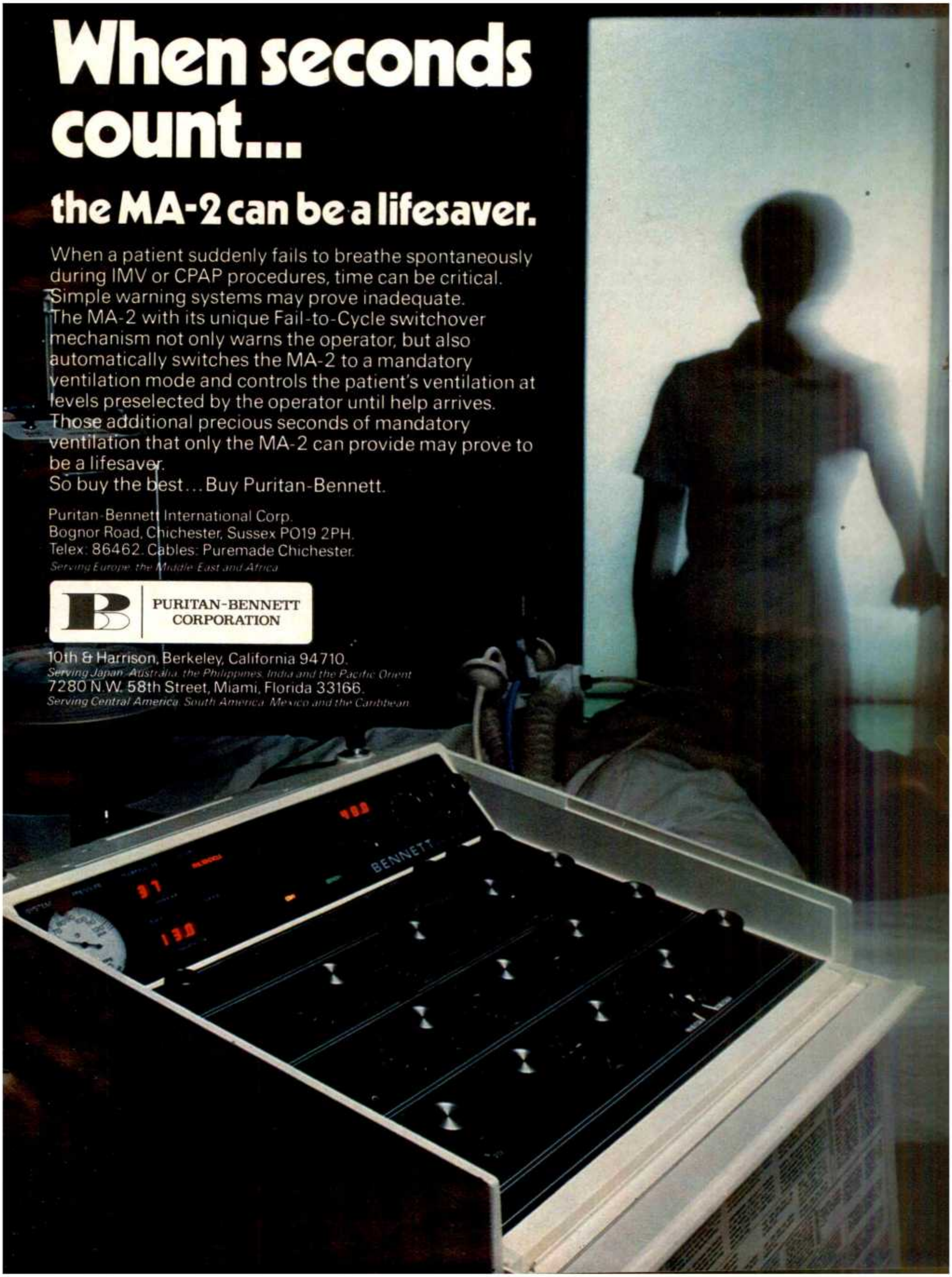

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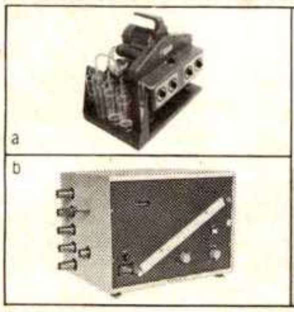

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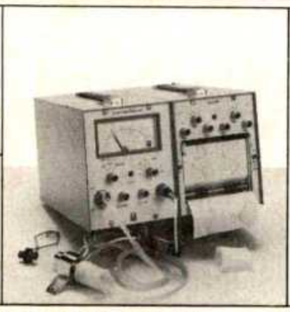

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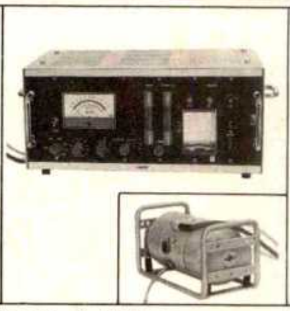

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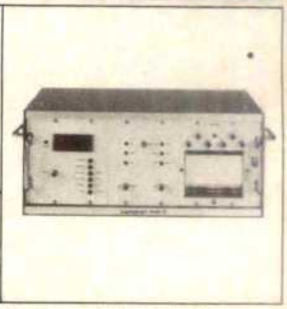

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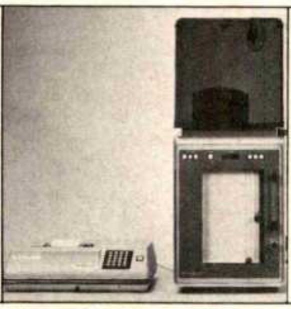

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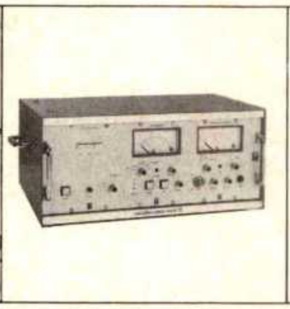

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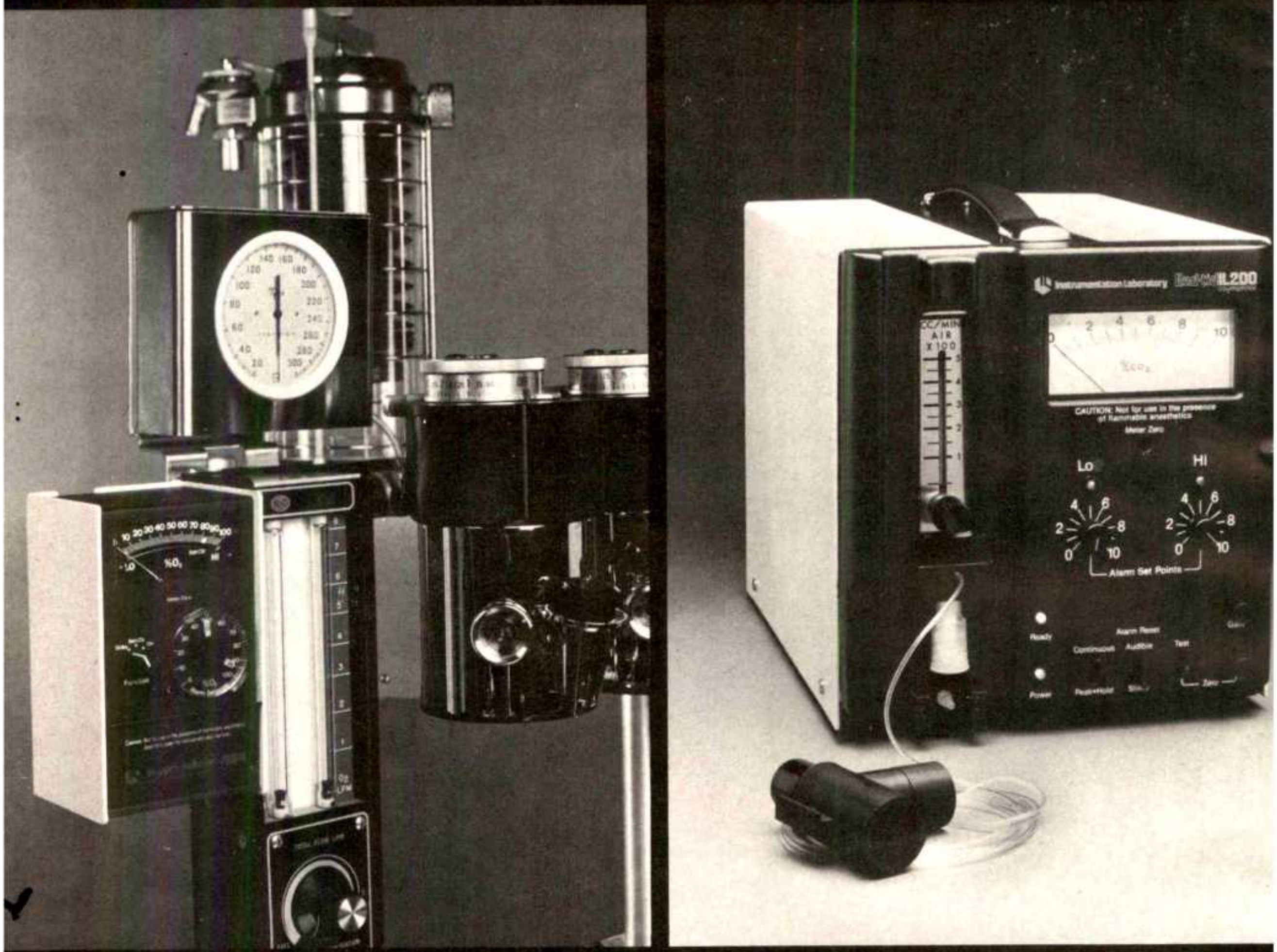

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 7 JULY 1980

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EDITORIAL

ANAESTHESIA FOR EYE SURGERY

Anaesthesia for eye surgery has been, and in some hospitals remains, a Cinderella of the anaesthetic services. Unlike many of the so-called anaesthetic specialties, ophthalmic anaesthesia has few devotees and, as far as we know, no one has formed a travelling club in its honour.

Yet there are aspects of the work which can stretch the clinical competence of even the most fully trained and skilled practitioner. Eye surgery may have to be undertaken as an emergency; in addition to the problems which attend all unplanned anaesthetics the patient whose eye has been penetrated as a result of injury will risk impairment or loss of vision if the anaesthetic is mismanaged. Similar risks occur when the eye is opened as part of surgical procedure in elective cases. Thus the anaesthetist must be familiar with the factors which control the volume and tension of the intraocular contents and the means by which these factors can be controlled if necessary.

Since the methods of control may result in disturbance of homeostatic mechanisms, for example deliberate hypotension, there is an added dimension to the problem of eye surgery in the large proportion of elderly patients with severe co-existing disease. On the other hand, for many anaesthetists the eye department may be the only place in which the skills for anaesthesia in young children and babies have to be exercised.

This symposium issue is an attempt to blend an account of the scientific principles which have to be mastered for the proper conduct of anaesthesia for eye surgery with personal statements by anaesthetists with considerable and special experience in this type of practice. That some of the content of the latter type may occasionally imply a difference of view between writers is not only a sign that there are, as in other types of practice, several ways of achieving the same objectives, but also that the possibilities for good clinical research in ophthalmic anaesthesia are by no means exhausted.

Alastair A. Spence

Br. J. Anaesth. (1980), 52, 643

THE CHANGING PATTERN OF EYE SURGERY

W. S. Foulds

One of the striking changes that has occurred in ophthalmology during the past 20 years or so has been the increasing use of general rather than local anaesthesia for the majority of ophthalmic operations. The change reflects improvements in both the techniques of ophthalmic surgery and anaesthesia. Thus previously, cataract wounds, for example, were left unsutured and healing was very dependent upon the immobility of the patient after operation and the avoidance of intraocular vascular congestion, such as might accompany retching or coughing, both of which were common concomitants of the general anaestheisa available at the time.

The introduction of fine suture materials and the use of the operating miscoscope in intraocular surgery allowed the development of accurate and watertight wound closure in the eye. Such wound closure had the advantages of mechanical strength and excellent tissue apposition, important considerations when one remembers that healing in ocular tissues must be optically as well as mechanically acceptable.

The immediate mechanical strength of an adequately sutured surgical wound in the eye has allowed ambulation of the patient very soon after operation, with a consequent decrease in the respiratory and other complications of bed rest which tend to beset elderly patients, and in addition has made acceptable the occasional instance of retching after operation, which in any case has greatly reduced in frequency with improved anaesthetic techniques.

The introduction of fine suture materials and the concomitant use of the operating microscope have been reflected, not only in an improvement in the techniques used for operations which were and are commonly performed, such as cataract extraction, but also in the development of new operative techniques for conditions previously considered not amenable to surgical treatment.

In the United Kingdom the three commonest causes of blindness are cataract, glaucoma and senile macular degeneration. Both cataract and glaucoma are frequently managed surgically. With regard to the latter condition, drugs which dilate the pupil and which may be used in premedication are often stated in manufacturers' literature to be contraindicated in patients with glaucoma. It is only in a few patients with the closed angle variety of glaucoma, however, that such drugs may have contraindications. In the majority of patients with glaucoma pupillary dilatation carries no risk.

In discussing changing patterns in eye surgery, the history of surgery for cataract is of interest.

Cataract is of course an opacity in the crystalline lens of the eye and in the majority of cases is an accompaniment of ageing. The condition is very common throughout the world and it is estimated that, in India alone, some 5 million people are blind from this potentially remediable cause.

From early times until the 19th century, a common procedure was the operation of couching, in which a sharp needle, or even a thorn, was inserted into the eye at the limbus and the cataractous lens dislocated posteriorly into the vitreous to clear the previously obstructed light pathway. The operation was quick and simple and could be performed without anaesthesia. Unfortunately, the dislocated lens frequently initiated a destructive inflammatory process within the eye and the visual results were poor.

In the early 19th centrury, the extracapsular technique for cataract extraction was evolved. Initially carried out with the operator facing the patient, the eye was opened inferiorly at the limbus with a triangular shaped knife, advantage being taken of the natural reflex elevation of the unanaesthetized eye to complete the incision and aid expression of cataractous material from the eye by pressure on the upper lid. Not unexpectedly, prolapse of other intraocular tissues, such as the iris and the vitreous was common and poor wound apposition and delayed healing further reduced the success rate, so that, for example in 1830, one of Sir William Bowman's Lectures given in the Royal London Ophthalmic

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W. S. Foulds, M.D., Ch.M., F.R.C.S., F.R.C.S. (Glas.), D.O., Tennent Institute of Ophthalmology, University of Glasgow, Western Infirmary, Glasgow G11 6NT.

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Hospital (now Moorfields Eye Hospital) was entitled "A Case of Cataract Extraction, Sight Remaining."

Gradually, the techniques were refined and following the introduction of topical cocaine and later of lid and ocular akinesia by facial nerve block and retrobulbar injection of local anaesthetic agents, the operation of extracapsular cataract extraction became safe and highly successful in the restoration of sight.

By this time, the technique involved an upper limbal incision with a conjunctival flap, removal of the anterior lens capsule by toothed forceps and careful delivery of the nucleus of the cataractous lens by pressure below and counter-pressure above the limbal opening, followed by irrigation of the anterior chamber to wash out some of the residual lens cortex, which had escaped expression. Healing of the wound was aided by the rapid adhesion which occurred between the replaced conjunctival flap and its bed, but wound strength was low and irregular healing of the wound with a poor optical result was common, as was the complication of iris prolapse, which if untreated could lead to destructive inflammation in the eye and other complications, including the loss of the fellow eye from sympathetic ophthalmitis.

The other disadvantage of the extracapsular technique was that it was only suitable for mature or "ripe" lenses and many patients had to accept severe visual disability for years before their cataract was considered suitable for surgery.

In the present century, the alternative technique of intracapsular extraction was developed and by the 1950's had supplanted extracapsular extraction as the standard operation for cataract.

In this technique, the suspensory ligament of the lens is ruptured and the whole lens, complete in its capsule, removed from the eye. Originally, the lens capsule was held by special forceps below its centre anteriorly and "tumbled" out of the eye—a manoeuvre not free from complications and later superseded by a refined technique in which the cataractous lens was slid from the eye following mechanical or later enzymatic rupture of the suspensory ligament.

The intracapsular technique required delicate judgement and while extracapsular extraction was easier to perform if the intraocular pressure was not too small, intracapsular extraction was greatly aided by a significant reduction in intraocular pressure, a condition which could readily be provided by the judicious employment of general anaesthesia. The ability of general anaesthesia to achieve a suitable reduction in intraocular pressure is one of the factors which has largely determined the use of general rather than local anaesthesia for the majority of intraocular operations where a normal or increased pressure always carries the risk of prolapse of vitreous or other intraocular structures.

The late 1950's saw the introduction of cryo-extraction, the lens being held and delivered from the eye by a probe which could be frozen to the surface of the cataractous lens. The use of cryo-extraction, the ability to carry out fine manipulations within the eye with the introduction of microsurgical instruments and the operating microscope, and not least the careful suturing of the cataract wound at the end of the operation has made this type of operation one of the safest and most rewarding operations in ophthalmic surgery.

Operating microscopes were first used by a few ENT surgeons early in the 20th century (Holmgren, 1917) and became popular for otological surgery in the 1940's, largely as a result of the influence of Lempert (1938). Some ophthalmologists started to use operating microscopes in the 1950's, but it was not until the present decade that ophthalmic opinion accepted the use of the operating microscope as being almost mandatory in intraocular surgery and particularly for the repair of penetrating ocular wounds.

Almost coincidental with the introduction of operating microscopes was the advent of fine suture materials, one of the earliest being virgin silk, which still retains a place in ophthalmic surgery. This natural material was followed by the introduction of synthetic monofilament sutures of 10/0 or even 14/0 gauge.

The control of intraocular pressure and ocular mobility provided by general anaesthesia and the enhanced view of the wound presented by modern operating microscopes, together with the development of fine instrumentation led, in the case of cataract extraction, first to the development of incisions which would heal with the minimum of optical distortion and later to the surgical correction of the inherent optical abnormalities which follow the removal of the lens. For the former, the development of stepped or angled corneal incisions with continuous suturing has involved the use of high magnification and precise surgical technique, using very sharp microsurgical knives which may even be diamond-tipped, or of mechanical cutting devices capable of making a regular incision of a predetermined depth and length. To correct the abnormal optics of aphakia, recourse has been had to the introduction into the eye of a plastic lens designed to take the place of the patient's own crystalline lens. Although an early attempt to use an artificial intraocular lens was pioneered in the United Kingdom by Ridley in 1951, it is only recently, with the development of newer microsurgical techniques, that this type of procedure has found acceptance and at present the surgical techniques are in a state of active experimentation and rapid evolution. Even now, selected patients can have near normal vision restored after cataract operation by the use of such an intraocular lens and we can look forward with some confidence to the perfection of this technique and its more general application.

Thus, cataract extraction has moved from what was a largely unsuccessful, often painful and distressing operation, to one in which near normal sight can almost be guaranteed. The introduction of newer techniques, however, has inevitably complicated the operation and increased the time required for its performance, factors which must be apparent to most anaesthetists involved in ocular surgery, particularly where junior ophthalmic staff are being taught the intricacies of microsurgery. The statement made by one anaesthetist colleague, that an operating microscope was a device introduced by ophthalmologists to make mountains out of molehills, is perhaps an over-emphasis of the penalties one must pay for improved techniques and results.

It is interesting that, as in most medical fields methods of treatment swing in and out of fashion, so in cataract extraction the carefully developed techniques for intracapsular lens removal are giving way to a re-introduction of the earlier extracapsular methods, largely because the preservation of the posterior lens capsule is helpful in stabilizing iris-fixed intraocular lenses and also because the introduction of new technology in the form of phako-emulsification now enables the extracapsular extraction of even an immature cataract through a minimal corneal wound. Phako-emulsification uses an ultrasonic probe to disintegrate the cataractous lens and a system of continuous infusion and suction to aspirate lens material from the eye while maintaining intraocular volume by a matched infusion of a suitably constituted aqueous substitute.

In glaucoma surgery and in corneal grafting, once again, general anaesthesia and microsurgical techniques have vastly improved the safety and success rate of surgery. In the past many graft failures which were ascribed to rejection are now known to have been caused by inadequate wound apposition, a source of graft failure which microsurgical instruments and improved suturing techniques have almost eliminated. Apart from the obvious use of corneal grafting in eliminating corneal opacity, modifications of the technique have been used to alter the optical characteristics of the eye and although keratomileusis, a technique designed to correct refractive errors, has not lived up to its initial expectation, this or modifications of it may well find an increasing place in the surgical management of refractive errors in the future. Keratomileusis involved the removal of a disc of cornea from the patient, its subsequent freezing and remodelling on a special lathe and eventual replacement of the remodelled and thawed disc back in the patient's cornea. Optically, the results were difficult to predict, especially in the long term, but interest in this field still continues.

In the early years of the present century ophthalmic surgery was virtually restricted to the anterior segment of the eye and conditions like retinal detachment were not amenable to treatment. In the 1920's Gonin in Lausanne recognized the crucial role played by retinal holes or tears in the genesis of retinal detachment and introduced the operation of galvanocautery whereby some retinal holes could be sealed and the accompanying detachment cured by perforation of the globe in the vicinity of the hole by an electrically heated probe (Gonin, 1934). This had the dual effect of releasing fluid from beneath the detached retina and of inducing an inflammatory reaction in the perforated choroid leading to retinal adhesion and closure of the hole. The success rate, however, was low—of the order of 20–30%—and prolonged bed-rest to keep the retina in apposition with its bed while healing occurred, was necessary. During the subsequent half-century the role of such factors as disparity between the volume of the eye and the detached retina and more particularly the essential role of the vitreous in the causation of retinal breaks and in providing a scaffolding for the unwanted ingrowth of collagen secreting cells has led to the development of more successful techniques for the treatment of retinal detachment. Indeed, the success rate for retinal detachment surgery is now of the order of 90%. This improvement in surgical results owes much to the use of binocular indirect ophthalmoscopy for the accurate localization of retinal breaks and to the use of ocular volume reducing operations, often utilizing a synthetic silicone rod, strap or sponge to produce a localized or encircling circumscleral indentation. There is still argument about the exact mechanisms whereby such operations work, but there is no argument about their high success rate.

In difficult cases of retinal detachment, internal tamponade of the retina may be achieved by the injection into the vitreous of air or other gases such as sulphur hexafluoride which expands after injection, or the injection of vitreous substitutes such as high viscosity silicone oil.

From the patient's point of view, double padding of the eye and prolonged bed rest are a thing of the past and the unfortunate sufferers from retinal detachment can look forward to a favourable outcome from surgery with a minimum of inconvenience before or after operation.

Until fairly recently, operations on the vitreous or on the choroid were considered impracticable and indeed the vitreous was regarded with a superstitious awe as being absolutely sacroscant, vitreous loss during cataract extraction, for example, frequently leading to disastrous visual loss.

One of the more exciting developments in intraocular surgery in recent years has been the realization that operations on the vitreous are not only technically possible, but often very rewarding. Thus, instrumentation has been developed which allows the ophthalmic surgeon to fragment and remove blood-stained vitreous, or dissect fibrous membranes within the vitreous cavity, by means of a complex cutting, sucking, infusing probe no more than 1–2 mm in diameter which can be passed through a small anterior incision in the eye and manipulated within the vitreous cavity under direct vision with an operating microscope using a contact lens to eliminate corneal refraction.

Such surgery demands patience and a delicate touch, and control of intraocular pressure and intraocular blood volume by suitable anaesthetic techniques is a prerequisite.

A rapid evolution of instrumentation, capable of being used within the eye to tackle problems in the vitreous, or even affecting the retina, has seen the introduction of ingenious instruments, all of which have in common a probe-like contour so that they can be passed through a scleral opening anteriorly and enter the vitreous cavity of the eye in front of the anterior insertion of the retina and behind the posterior edge of the very vascular ciliary body. They are either cannulated or used in conjunction with a separate intraocular cannula, fed from a reservoir so that their use is always within a closed eye maintained at near normal intraocular pressure. Such instruments have included intravitreal bipolar diathermy probes for sealing abnormal vessels in the vitreous or on the optic nerve head, fine intravitreal scissors or guillotines, intravitreal fibreoptic lighting devices, intravitreal infusing or illuminating picks, designed to dissect fine fibrous membranes from the surface of the retina and even intravitreal photocoagulating devices designed to photocoagulate the retina under direct vision during the course of vitreous surgery.

One of the main indications for the use of such instrumentation is in the management of the retinal complications of diabetes, so often characterized by neovascularization within the eye leading to vitreous haemorrhage, fibrous proliferation and traction retinal detachment. The instruments are well adapted to the removal of tissues from both the posterior and the anterior segment of the eye and are finding increasing application in reconstruction of the anterior segment of eyes damaged by penetrating trauma such as one sees in windscreen injuries and even in the removal of cataractous lenses, particularly those complicating long-standing inflammation in the eye or those presenting as congenital defects.

Undoubtedly, we are still at an early stage in exploring the possibilities of this type of surgery and we can anticipate continuing refinement in instrumentation and technique, allowing even more daring surgery on the retina itself and on other intraocular structures.

A personal interest has been the surgical management of intraocular malignancy such as melanoma of the choroid or ciliary body. Techniques are now available for the local excision of even quite large tumours from the eye with the retention of a functioning organ and as far as we can tell no worsening of the prognosis for survival of the patient. The choroid and ciliary body are extremely vascular and surgery to these tissues necessitates the bloodless field which can be provided by carefully controlled hypotensive anaesthesia. Again, the localization of the tumour within the eye and its careful dissection under high magnification using an operating microscope demands patience and time, on the part of both the operator and the anaesthetist who is such a vital part of the team in this as in many forms of ocular surgery.

Experience during the past 10 years suggests that further development of techniques for local excision of malignant tumours from the eye is possible and one is constantly surprised at how much in the way of surgical interference, if carefully planned and applied, the human eye will tolerate.

Little has been said so far about extraocular surgery, although undoubtedly advances have been made in techniques for the plastic reconstruction of the lids, the correction of ocular muscle imbalance and in lachrymal surgery. These advances, while rewarding, have perhaps not been so spectacular as those affecting intraocular surgery, with perhaps the exception of orbital surgery, which once again is coming back into the domain of the ophthalmic surgeon rather than of the neurosurgeon. In orbital surgery, hypotensive anaesthesia and control of bleeding are invaluable in aiding the delicate dissections required for the identification and localization of the numerous important structures which lie crowded together in this small area, so that damage to them can be avoided during, for example, the mobilization and removal of an intraorbital tumour. The lateral approach to the orbit with a replaceable bone flap can allow access to all parts of the orbit and is now the approach of choice for the majority of intraorbital lesions requiring surgical intervention.

A combination of improved technology, as regards both instrumentation and visualization of the operative field, combined with the imaginative use of the techniques available now allows the ophthalmic surgeon to move freely in the orbit and within the eye to perform reconstructive surgery or deal with abnormalities, using techniques which a few years ago would have been thought to be wild imaginings. The role of the anaesthetist has been crucial in these advances and together we can confidently look forward to even more remarkable therapeutic innovations in the future.

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FUNCTIONAL ORGANIZATION OF THE HUMAN EYE

J. L. JAY

The human eye is a highly specialized sensory organ which is sensitive to radiant energy in the spectral range 400–760 nm which we therefore term the visible spectrum. The retina itself is sensitive to a wider range, including 350–400 nm, but these wavelengths are usually absorbed in passage through the transparent optical media of the eye, especially the crystalline lens. The functional organization of the eye may be divided for descriptive purposes into a telereceptor or sensory system which converts incident light energy to bio-electric signals for transmission to the occipital cortex, a refractive system to focus a sharp retinal image of external objects and various support systems to maintain the structural integrity, nutrition and defence mechanisms of the eyeball.

STRUCTURAL ARRANGEMENT OF THE HUMAN EYE

The eye is approximately spherical, with an external diameter of 24 mm and the coats are arranged in three layers (fig. 1). The opaque, white, outer layer—the sclera—is the main structural component and continues into the cornea over the anterior one-sixth of the globe. It is of limited elasticity after infancy, but remains soft and flexible unless maintained in an inflated condition by an intraocular hydrostatic pressure greater than the tissue pressure in the orbit. This flexible exoskeleton receives the tendinous insertions of the external ocular muscles whose contractions produce movement of the eyeball and cause transient fluctuations in intraocular pressure. The sclera consists of dense collagen bundles and varies in thickness from 0.3 mm under the insertions of the rectus muscles to 1 mm just behind the limbus. Although avascular, it is pierced by the anterior and posterior ciliary arteries and nerves and also the emergent vortex veins. The central retinal artery and vein pass through the sclera with the optic nerve axons at the lamina cribrosa.

The middle coat, the vascular and pigmented uvea, is applied to the inner surface of the sclera except at the optic nerve and posteriorly consists of the choroid running forwards into the ciliary body. This contains the ciliary muscle which controls the curvature of the crystalline lens during accommodation, when its circular contraction releases tension on the suspensory ligament of the lens and allows the lens to assume a more convex shape for focusing on near objects. The radial folds on the inner surface of the ciliary body, the ciliary processes, are the site of formation and secretion of the aqueous humour. The iris is the forward extension of the ciliary body and forms a variable aperture diaphragm which adjusts to control retinal illumination and also reduces optical aberrations from light rays passing through the peripheral parts of the cornea and lens. The discrete smooth muscle ring of the sphincter pupillae lies behind the pupil margin while its antagonist, the dilator pupillae, is an ill-defined arrangement of radial fibres on the posterior surface of the iris. Parasympathetic stimulation produces constriction of the sphincter pupillae and ciliary muscle. The parasympathetic fibres arise from the Edinger–Westphal nucleus and run with the oculomotor nerve to synapse in the ciliary ganglion just behind the eyeball. They then pierce the coats of the eye in the short ciliary nerves and run forward in the choroid to reach their destination. The sympathetic fibres, which produce dilatation of the pupil and supply the ocular blood vessels, synapse in the superior cervical ganglion and reach the eye by way of the carotid plexus to join the long and short posterior ciliary nerves.

The third and innermost coat, the retina, is a neuro-ectodermal tissue structured in many layers from the outermost pigment epithelium to the innermost nerve fibre layer (fig. 2). The photoreceptors are applied to the pigment epithelium and comprise the rods, whose pigment, rhodopsin, is monochromatically sensitive to low light intensity and the less numerous cones, sensitive to greater levels of illumination. The cones are of three populations each with its own colour-sensitive pigment, erythrolabe, chlorolabe or cyanolabe, and are confined to the area around the macula which subtends the central area of visual field. The interconnections of

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0007-0912/80/070649-06 $01.00

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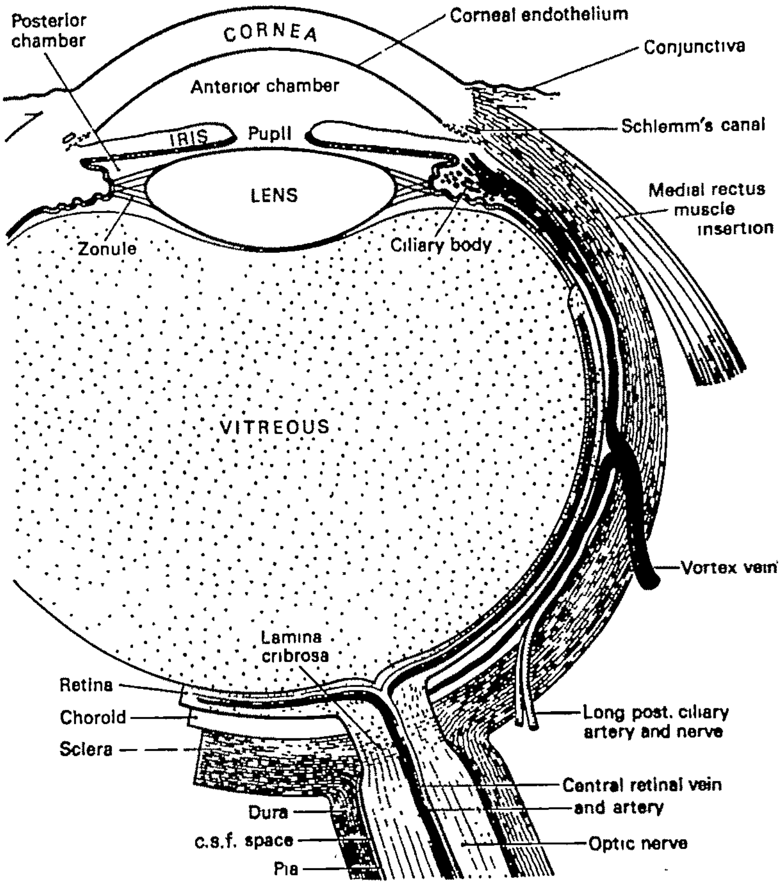

FIG. 1. Cross-sectional diagram of the human eye.

the cones are more complex than those of the rods and so the cone system provides the most detailed perception of form and movement. The retinal photoreceptors therefore function as photo-chemico-electric transducers connected to cell circuits which provide lateral integration and digital coding before transmission along the axons in the nerve fibre layer to the optic nerve and onward to the higher visual centres. Anteriorly the retina continues as a double-layered epithelium over the pars plana of the ciliary body and then over the ciliary processes where it is specialized for the secretion of aqueous. Finally, this layer passes onto the posterior surface of the iris as a heavily pigmented double epithelium.

THE REFRACTIVE SYSTEM

The remaining structures of the eyeball are transparent and avascular so that light may be transmitted to the retina. In addition the various interfaces between the optical media—air, cornea, aqueous, lens and vitreous—must be of regular surface curvature of combined refractive power to form an undistorted and sharply focused image on the retina.

The cornea remains transparent by virtue of the regular lattice arrangements of its collagen bundles so that rays diffracted from their original direction are eliminated by regular interference. The regular spacing of the layers of collagen bundles is therefore critical and depends on the metabolic activity of the endothelial cell monolayer on the posterior corneal surface. These cells have an active transport system transferring bicarbonate ions from cornea into the aqueous humour with secondary ion fluxes maintaining the corneal stroma slightly less hydrated than other tissues. If this function is lost the cornea swells and loses transparency. The outer surface of the cornea is covered by stratified squamous epithelium which is, in its turn, coated with a tear film of complex construction maintaining a protective fluid surface on the hydrophobic surface membrane of the

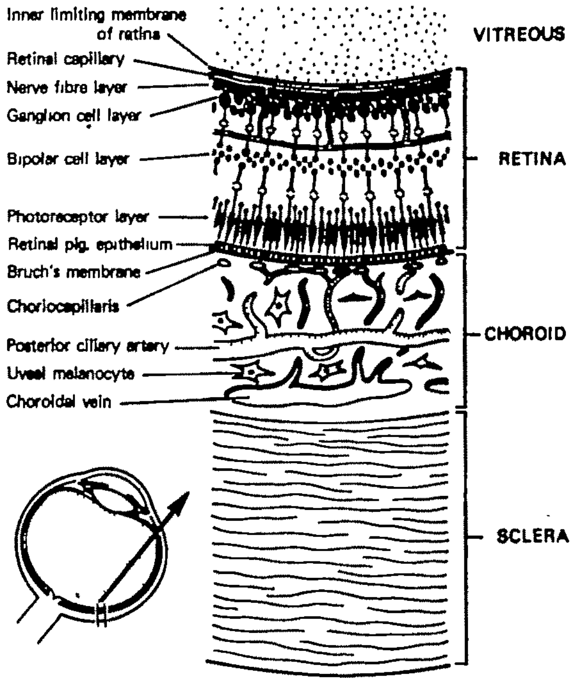

FIG 2. Structural detail of the coats of the eye.

epithelium. The epithelium is richly supplied with pain-sensitive nerve endings essential for corneal protection.

The crystalline lens is bathed in aqueous humour and lies behind the pupil, connected to the ciliary body by the suspensory ligament or zonule. Enclosed in an elastic capsule, the shape and therefore the optical power of the lens varies with the tension in the zonule depending on the amount of constriction of the ciliary muscle. The optical clarity of the lens is maintained by the metabolic activity of the epithelium which lies behind the anterior capsule. These cells divide throughout life and migrate, losing their nuclei, to form new cortical lens fibres at the periphery of the lens.

Behind the lens and filling the posterior segment of the globe is the vitreous body, a hyaluronic acid gel loosely structured in a delicate network of collagen fibrils which allows passive transfer of water and solutes. The vitreous is attached to the retina around the ciliary body and optic disc but lies in loose apposition in other areas.

THE NUTRIENT SYSTEMS

The coats of the eye receive blood from the ophthalmic branch of the internal carotid artery via the anterior and posterior ciliary arteries and the central artery of the retina, but the vascular arrangement is rather complex (fig. 3). The transparent optical media, however, remain avascular and the metabolic requirements of these structures are met by the formation and circulation of the aqueous humour, a transparent cell-free secretion from the ciliary processes.

Arterial supply

The uveal coat is a highly vascular structure in which there is anastomosis between the anterior ciliary arteries and the long and short posterior ciliary arteries. The iris is supplied by about seven anterior ciliary arteries which run with the rectus muscles and pierce the sclera a short distance behind the limbus to form an anastomotic ring, the major arterial circle of the iris, at the junction of iris and

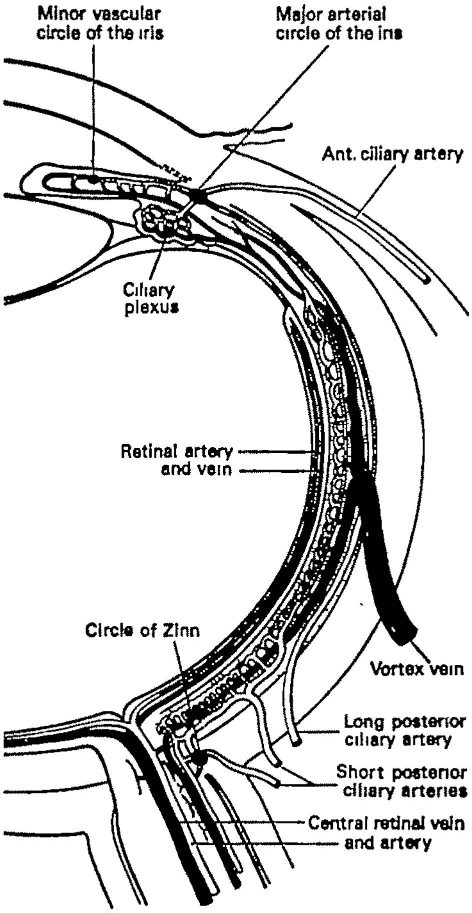
Minor vascular circle of the iris
Major arterial circle of the iris
Ant. ciliary artery
Ciliary plexus
Retinal artery and vein
Circle of Zinn
Vortex vein
Long posterior ciliary artery
Short posterior ciliary arteries
Central retinal vein and artery

FIG. 3. The vascular supply of the eyeball.

ciliary body. This ring also receives the terminal branches of the two long posterior ciliary arteries running forward in the choroid and sends radial branches into the iris which communicate in the lesser vascular circle of the iris about two-thirds of the distance towards the pupil. It also sends branches posteriorly to the ciliary body to join the vascular plexus in the ciliary processes. Almost a dozen short posterior ciliary arteries pass through the sclera near the posterior pole of the eye in company with the two long posterior ciliary arteries, but while the latter run forwards to the ciliary body the short posterior ciliary arteries branch at once and form a profuse capillary network, the choriocapillaris, on the inner surface of the choroid. The capillaries are embedded in Bruch's membrane, on which lies the retinal pigment epithelium and they provide the essential vascular supply for the photoreceptors and outer one-third of the retina. Anteriorly, the terminal branches of the short posterior ciliary arteries anastomose in the ciliary body with the branches of the major circle of the iris, and around the optic nerve head its branches form a circular anastomosis, the circle of Zinn, which supplies the anterior part of the optic nerve. There may be an inconstant anastomosis between the short posterior ciliary arteries and branches of the central retinal artery in front of the lamina cribrosa, but not infrequently a branch of the short posterior ciliary arteries, the cilio–retinal artery, supplies an area of retina adjacent to the optic disc. The central artery of the retina enters the optic nerve after crossing the cerebrospinal fluid space approximately 12 mm behind the globe and, running forwards without contributing significantly to the blood supply of the nerve, it divides on the optic disc into four branches which supply the inner two-thirds of the retina, leaving an avascular area at the macula.

Venous drainage

Most of the blood from iris, ciliary body and choroid drains to the four vortex veins which pass through the sclera behind the equator and join the venous plexuses of the orbit, finally reaching the cavernous sinus. Only a small proportion of the intraocular circulation drains anteriorly through the sclera to join the episcleral and sub-conjunctival veins. Tributaries of the central retinal vein return along the course of the central retinal artery. No lymphatic drainage can be identified in the eye.

Although the total choroidal blood volume is small, this tissue is little more than a dense network of blood vessels and the blood flow per gram of tissue is one of the greatest in the body, comparable to that of the liver. Moreover, the choroidal blood volume may vary considerably, even doubling or trebling the thickness of that layer with a resultant constricting effect on the posterior vitreous, forcing it forwards into the surgical field when the eye is open during cataract operations. If the globe is intact, then fluctuations in uveal blood volume will have profound effects on the intraocular pressure. The arterial flow in the choroid is subject to local autoregulation and, as in the cerebral circulation, hypercapnia produces vasodilatation. In addition to factors influencing arterial calibre, the effect of squeezing vitreous into the anterior surgical field is enhanced by factors producing venous congestion in the head and neck, with resultant increase in orbital and ocular venous pressure.

Aqueous humour

This transparent fluid is not unlike plasma in its ionic composition, but has a very small protein content and a large concentration of ascorbic acid. It is produced from the plasma filtrate from the ciliary plexus by an active transport system in the non-pigmented outer layer of the epithelium covering the ciliary processes. The aqueous circulates in the anterior segment of the eye (fig. 4), bathing lens and cornea and exchanging water and solutes with the vitreous humour. Approximately 1.3 μlitre min^{-1} is secreted into the posterior chamber, passing through the pupil into the anterior chamber where it reaches the angle between iris and cornea and returns to the venous circulation by passing through the specialized drainage apparatus comprising the trabecular meshwork, Schlemm's canal and the intrascleral collector channels. The trabecular meshwork is an open net of collagen bundles covered by endothelial cells con-

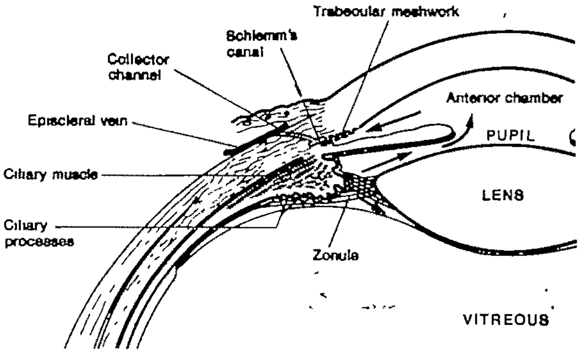

FIG. 4. The circulation and drainage of the aqueous humour.

tinuous with the corneal endothelium. The aqueous first enters the relatively coarse uveal portion and then passes through the finer spaces of the deeper corneo–scleral meshwork to arrive at the endothelium of Schlemm's canal. It must cross this barrier by a process of transcellular vacuolation before reaching the lumen of Schlemm's canal itself. The canal is a circular channel similar to a venule which runs round the corneo–scleral junction or limbus and drains into the episcleral venous plexus by way of numerous radial collector channels. In addition, about 10% of aqueous drainage occurs by passing into iris tissue and on via the suprachoroidal space to traverse the sclera. This uveo–scleral component of drainage is not subject to compensatory adjustments.

REGULATION OF INTRAOCULAR PRESSURE

If the eyeball is not to collapse, then the balance of production and drainage of aqueous humour must maintain an intraocular pressure greater than that exerted on the globe by the orbital tissues. Given our understanding of physiological control systems, it is inconceivable that some form of pressure-sensitive feed-back does not exist. Yet the nature of this control system or indeed its location, whether within the eye, the orbit or the central nervous system, remains a mystery. In the healthy eye the intraocular pressure fluctuates narrowly between 15 mm Hg and 20 mm Hg and the two eyes of an individual seldom differ by more than 5 mm Hg. The formation of aqueous humour is relatively constant in most circumstances, but the drainage capacity is capable of wide variation, so that factors acting to increase or decrease the intraocular pressure will create a transient swing in pressure, rapidly damped by the adaptation of the outflow facility. If, however, this outflow facility is restricted, as it is in various forms of glaucoma and unidentified pre-glaucoma conditions, then factors producing an increase in intraocular pressure will have exaggerated and prolonged effects.

Neuro-pharmacological influences

Parasympathetic stimulation or topical application of acetylcholine and other cholinergic agents are associated with a marked increase in the facility of aqueous outflow mediated by the contraction of the ciliary muscle, which increases the spaces between the beams of the trabecular meshwork. Similar topical application of both sympathomimetic agents such as adrenaline and, paradoxically, sympatholytic agents such as guanethidine or beta-blockers is associated with a decrease in aqueous production. Although these pharmological agents are used clinically to reduce intraocular pressure, their importance in the normal regulation of intraocular pressure remains uncertain.

Adrenocortical steroids

There is a diurnal fluctuation in the rate of aqueous secretion which is probably linked to the circadian rhythm in the secretion of endogenous adrenocortical steroids, so that the intraocular pressure reaches a peak in the early morning from a trough in the late afternoon. Exogenous steroids applied as eyedrops will often produce an increase in intraocular pressure after several weeks of use and this is associated with a decreased facility for aqueous drainage. This steroid response is familial and inherited as an autosomal recessive trait. Steroids taken systemically are very much less likely to produce this response.

Vascular factors

Changes in intravascular pressure and volume within the uvea appreciably affect the intraocular pressure, but changes in the orbital vessels may produce similar effects. Most of these fluctuations exert their influence by varying the constrictive force on the intraocular fluids and so these changes will be compensated by increased or decreased aqueous drainage. Specific vascular changes may, however, produce permanent change in intraocular pressure if they also have a direct effect on the production or drainage of aqueous. Thus, when there is a profound reduction in the perfusion of the ciliary body, the aqueous production may be reduced beyond the level at which outflow adaptation can maintain a normal intraocular pressure. Conversely, increase in the episcleral venous pressure is directly transmitted to Schlemm's canal, so that the facility for aqueous drainage is restricted, causing increase in the intraocular pressure.

It is difficult to be sure of the exact relationship of systemic arterial pressure to uveal volume and blood flow as low perfusion may be modified by the effects of local autoregulation, but the systolic arterial pulse is certainly accompanied by a transient increase in intraocular pressure and arterial hypotension produces a decrease in intraocular pressure. Increase in central venous pressure is accompanied by an increase in intraocular pressure and this is seen with the fluctuation of intraocular pressure with inspiration and expiration, as well as the slight increase when changing from the erect to supine posture. Venous pressure effects probably act by constriction of the intraocular contents, but the specific effect of increased episcleral venous pressure in reducing aqueous outflow will limit the ability of the eye to compensate for the constrictive effect.

In addition to these changes in vascular hydrostatic pressure, the intravascular osmotic pressure may influence the intraocular pressure if the tonicity of the intravascular compartment is sufficiently increased to draw water from the extravascular compartments within the eye and orbit. Thus in severe diabetic keto-acidosis the eyes may occasionally be so hypotonic that the corneas become concave.

Mechanical factors

The globe is continuously subject to non-vascular mechanical influences which cause transient fluctuations in intraocular pressure. During eye movements the pull of the extraocular muscles on the sclera causes surges in intraocular pressure and a similar effect is produced by the eyelids during tight closure, although this latter effect may be enhanced by the associated contraction of the superior rectus muscle.

It is important to avoid increase of the intraocular pressure before making a surgical incision in the eye, as sudden ocular decompression may provoke intraocular haemorrhage or prolapse of intraocular tissue, but once the eye has been opened (whether by a surgical or traumatic wound) the various influences which act directly on formation or drainage of aqueous humour become relatively unimportant. There remain, however, the factors described above which act indirectly by vascular constriction of intraocular contents or mechanical distortion of the globe, and if these remain uncontrolled there is a continuing risk of extrusion of the contents of the eye.

ACKNOWLEDGEMENTS

I should like to thank Mrs Priscilla Miles, D.A., for preparing the illustrations and Miss Olive M. Rankin for typing the manuscript.

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Br. J. Anaesth. (1980), **52**, 655

ASPECTS OF MEASUREMENT IN OPHTHALMOLOGY

M. LEMAY

Blood supply

The blood supply to the eye differs in a number of respects from that to other organs in the body. The retina is a part of the brain and is connected to the brain by the optic nerves. The term "optic nerve" is incorrect, as it is in reality a cerebral tract connecting one part of the brain to another. The retinal blood supply is therefore similar to the cerebral blood supply and nutrition of the retina is accomplished from the retinal capillary beds by glial cells, which transfer nutrients directly from the vascular lumen. In the systemic circulation nutrition of body cells is accomplished by the extracellular fluid and removal of this fluid is effected by veins and lymphatics. The retina, in common with brain tissue, has no lymphatic supply. The blood supply to the inner two-thirds of the retina is by the central retinal artery, an end artery derived from the internal carotid via the ophthalmic artery. The retina contains two major capillary beds at different levels, supplied by the branches of the central retinal artery. The outer one-third of the retina is supplied by diffusion from the choroid, or middle coat of the eye. The choroid derives its blood supply from multiple small vessels which pierce the sclera posteriorly and provide a segmental blood supply to the choroidal capillary bed. There are between 10 and 20 short posterior ciliary arteries supplying the posterior choroid and prelaminar optic nerve head. These are derived from two or three main posterior ciliary arteries, which in turn are branches of the ophthalmic artery. Two of the posterior ciliary arteries derived from the main posterior ciliary arteries run forward in the suprachoroidal space between the choroid and the sclera. These may supply small segments of the choroid laterally and medially (Hayreh, 1976), but mainly terminate by forming the major arterial circle of the iris in the anterior ciliary body.

The ophthalmic artery gives branches to the extraocular muscles in the posterior orbit and anteriorly these vessels enter the globe at the attachments of the muscles. At this point, they are known as the anterior ciliary arteries. The anterior ciliary arteries also terminate at the major circle of the iris. The blood supply to the anterior segment and ciliary body is derived from the conjunctival, anterior ciliary and long posterior ciliary arteries.

The venous drainage of the eye mirrors the arterial supply, but there is no major venous circle within the iris. The venous anastomosis is less well defined and its situation closer to the pupil is responsible for its having been named the "minor vascular circle of the iris". The inner retina drains into the central retinal vein, which crosses the dural spaces before leaving the optic nerve sheath posterior to the globe. At this point, the vein can be compressed by increased cerebro-spinal fluid pressure and swelling of the optic nerve head may result. The choroidal venous drainage is through the vortex veins, situated in the four quadrants of the eye, just behind the equator. The fact that there are up to 20 arteries supplying the choroid and only four main veins means that ischaemic areas of the choroid may fill by retrograde flow through the venous channels (Hayreh, 1976).

Formation and drainage of aqueous

The aqueous humour is produced in the posterior chamber of the eye and flows through the pupil into the anterior chamber where it passes out of the eye through the trabecular meshwork. The trabecular meshwork is situated in the angle of the anterior chamber between the peripheral cornea and iris. The resistance to flow in the trabecular tissue probably maintains the intraocular pressure (i.o.p.) within physiological values, but the mechanism of homeostasis is unknown. The aqueous drains into the venous system via the canal of Schlemm, then into aqueous veins in the episcleral tissue. The episcleral veins drain into the orbital venous system and eventually to the cavernous sinus via the superior and inferior ophthalmic veins. A gradient normally exists between i.o.p. and the pressure within the aqueous veins; intraocular pressure may increase if episcleral venous pressure is increased.

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0007-0912/80/070655-08 $01.00

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TABLE I. *Causes of increased intraocular pressure (i.o.p.)*

Disease or disturbance	Increase in i.o.p.	Clinical condition
Congenital abnormality of the eye	Variable, variable age of onset	Congenital glaucoma Developmental glaucoma
Degenerative disease of trabecular meshwork	Chronic, asymptomatic, moderate	Chronic simple glaucoma (open angle glaucoma)
Anatomical shallow anterior chamber with large anteriorly placed lens. Leads to pupillary block to aqueous and closure of the angle by iris	Acute, severe	Acute glaucoma (closed angle glaucoma)
Blockage of trabecular meshwork by debris	Variable	Pseudoexfoliation syndrome Pigmentary glaucoma Glaucoma secondary to iritis Hyphaema
Increase in episcleral venous pressure	Moderate	Orbital tumours or haemorrhage Carotico-caverous fistula ? Dysthyroid exophthalmos
Steroids ? Oedema of meshwork	Variable	Steroid-induced glaucoma

In some disease states, an increase in intraocular pressure may occur in a number of situations (table I). The term "glaucoma" is applied to any condition causing increased i.o.p. Any chronic increase in pressure in the eye will in turn damage the trabecular meshwork and may exacerbate the situation (Lee and Grierson, 1974). Chronic forms of glaucoma may therefore develop as a result of degeneration in the trabecular meshwork or because of meshwork degeneration following prolonged increase of intraocular pressure for other reasons.

CLINICAL MEASUREMENT

Measurement of intraocular pressure

The accurate regulation of intraocular pressure is necessary to maintain the shape of the eye for optical purposes. Too small a pressure will enable external forces to compress and distort the eye and may permit the development of unwanted oedema; too great a pressure will prevent perfusion of the eye with blood. The eye is a closed organ and the analogy of intracranial pressure is often used to assist understanding of ocular fluid dynamics. The aqueous humour, in addition to its supportive role, is also nutritive to the cornea and to the lens. There is therefore an active turnover of aqueous in order that the nutritive functions can be maintained. Like cerebrospinal fluid pressure, i.o.p. is the result of the balance between inflow and outflow and increase or decrease in i.o.p. may reflect change in either. Aqueous is produced by the ciliary epithelium as a result of ultrafiltration of plasma by hydrostatic pressure and by the process of active transport of sodium ions into the posterior chamber. This active transport is responsible for the subsequent inflow of water into the posterior chamber along the resultant osmotic gradient. Assuming a constant rate of aqueous inflow, the intraocular pressure is therefore dependent on the outflow resistance offered by the trabecular tissue, and outflow of aqueous assumes a pressure gradient between i.o.p. and the episcleral venous pressure. External pressure on the eye will obviously increase i.o.p. initially, but even if the compression is maintained, aqueous outflow will cause a decrease in i.o.p. and regulation at the previous pressure should ensue. Measurement of i.o.p. should therefore give information relating to the relative amounts of aqueous inflow and aqueous outflow and should enable some conclusions regarding the normality of aqueous production and aqueous drainage. Like arterial pressure, i.o.p. can be measured manometrically (directly) or tonometrically (indirectly, by inference). Manometric measurement of i.o.p., when the anterior chamber is cannulated, is not used clinically and the method is restricted to experimental work. Indirect methods of measurement, therefore, are important. Historically, indentation of the eye was practised through the eyelid and on the

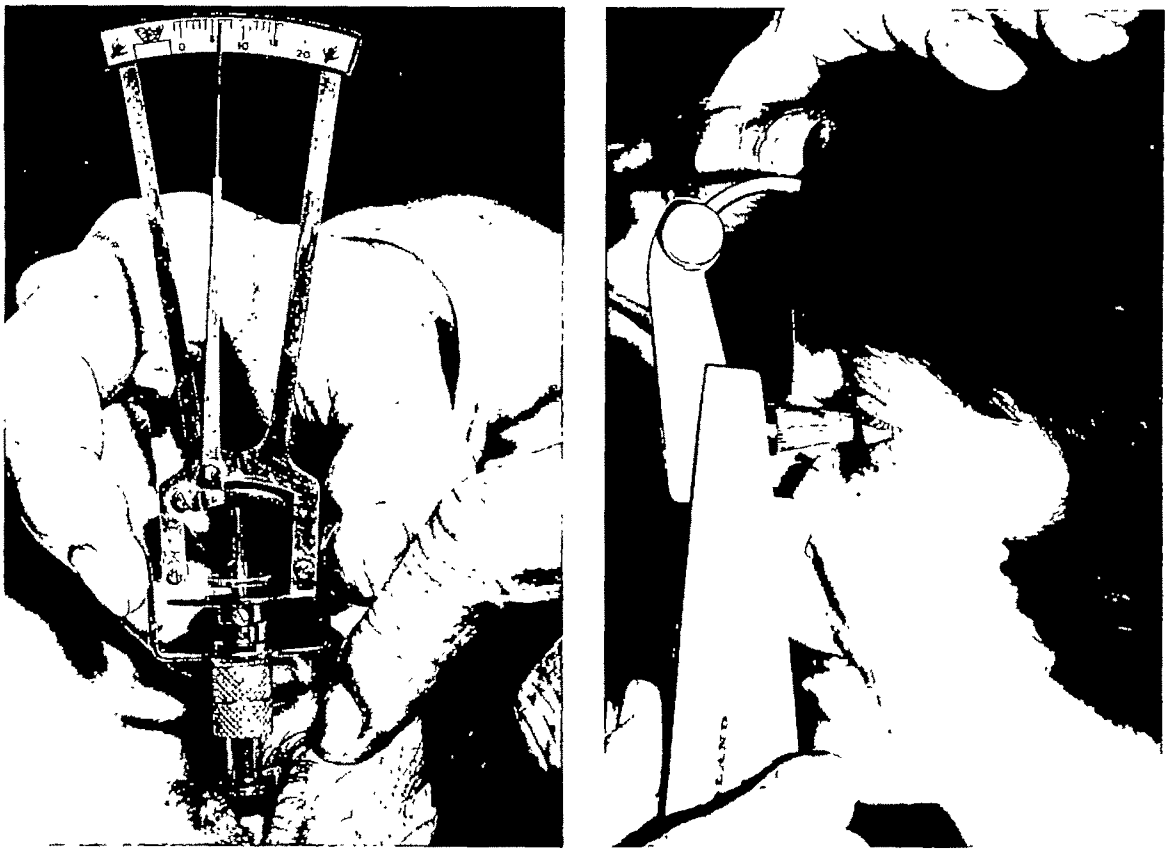

FIG. 1. The Schiøtz Tonometer (left). This is an example of an indentation tonometer. The scale does not give a direct reading of intraocular pressure, which is found by consulting a separate table. The Perkins Tonometer (right) is a hand-held applanation tonometer and gives an accurate reading directly from the scale.

sclera, but more recently instruments have been applied to the cornea, usually requiring corneal anaesthesia. There are two basic methods of measuring i.o.p. indirectly. Both depend on the application of a measured force to the eye and the resulting deformation. In one, the amount of indentation produced by a given force is measured, and in another the area of flattening is noted (applanation). All tonometers increase i.o.p. and the measured pressure is greater than the pressure before tonometry. The rigidity of the wall of the eye is an additional complicating factor to oppose the applied weight and may cause inaccuracy.

The ophthalmic literature contains many references to new tonometers, but several have remained in common use. The Schiøtz tonometer (Schiøtz, 1920, 1925) is the most widely used indentation tonometer, but is inaccurate because of wide variations in scleral rigidity (Friedenwald, 1957). Repeated measurements with different loading weights are required to calculate correcting coefficients and improve the accuracy. The Schiøtz method remains in common use despite its inaccuracy, and it must be said in its favour that it is easy to use and is therefore a useful instrument for semi-skilled personnel (fig. 1). The most widely used instrument is the applanation tonometer in one of its many forms. Significant improvement in accuracy can be achieved by the applanation of a standard area of cornea. The tonometer is in contact with the tear film and the area of applanation is usually visualized by the addition of a dye to the tear film and observation of the flattened and therefore dye-free area. With small areas of applanation, the surface tension of the tears makes the area of flattening greater than expected and with large areas of applanation, corneal rigidity makes the area of flattening less. An intermediate area of flattening is adopted therefore, and in the Goldmann Tonometer, an area 3.06 mm in diameter is chosen. This instrument only displaces a small volume of aqueous and the small increase in i.o.p. produced makes the Goldmann tonometer one of the easiest to calibrate and the most accurate in use. A portable tonometer has been devised by Perkins (Perkins, 1965), utilizing the Goldmann tonometer head. By the use of a split-prism doubling device in the optics of the tonometer (Perkins, 1965; Draeger, 1967), the end-point of the tonometer is easily visualized and the device is quick and easy to use. Because of its accuracy and ease of use the Perkins tonometer has been popular for assessment of intraocular pressure during anaesthesia (Al-Abrak and Samuel, 1974; Samuel and Beaugié, 1974). The Mackay-Marg electronic tonometer has attempted to eliminate the problems of the forces of rigidity and surface tension and has the advantage of producing a permanent graphic record (Mackay and Marg, 1959). This instrument contains a small plunger in the tonometer head the movements of which are recorded graphically during a rapid application to the cornea. The equipment is cumbersome and requires experience to obtain satisfactory readings.

Finally, the most recent development is the no-contact or air tonometer (Langham and McArthy, 1968). Corneal flattening is produced by a strong jet of air of constant known force. This jet is directed at the central cornea from a fixed distance. The optics of the system ensure that the air jet is normal to the cornea. A photocell measures the reflection of an incident beam of light from the cornea. At the moment of corneal flattening the reflected light increases; the amount of the increase is inversely proportional to the intraocular pressure, and the value for i.o.p. is calculated electronically. The air tonometer was developed for the American market where opticians and other non-medical personnel are not permitted to apply instruments to the cornea or to instill topical anaesthetics. This tonometer is accurate, but can be used only on a mobile patient and in the erect position. The cornea must be smooth and normally reflective.

The air tonometer is favoured by some opticians in the United Kingdom, but it is expensive and the lack of legal restraints on the use of alternative instruments have limited wider adoption.

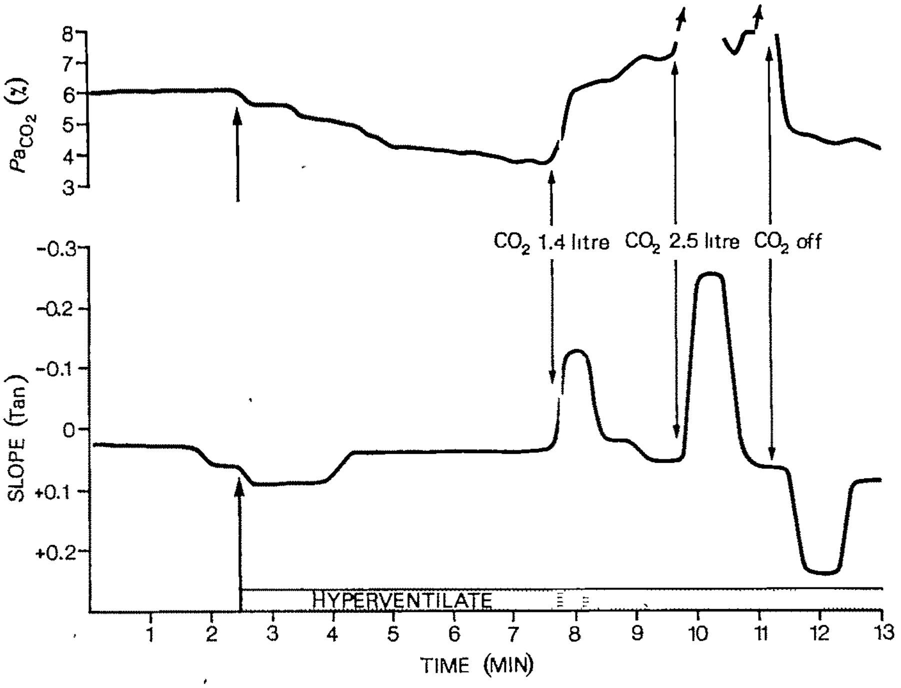

FIG. 2. Demonstration of rapid changes in ocular fluid dynamics with variation in end-expired P_{CO_2}. The tonography gradient is steeper with decreasing carbon dioxide and reverses with large increases.

Tonography

Tonography is a technique which was introduced for the clinical assessment of patients with glaucoma. If serial readings are taken with the Schiøtz indentation tonometer, successive values for i.o.p. are smaller because of the displacement of aqueous through the normal drainage channels. By utilizing electronic versions of the Schiøtz tonometer, a continuous reading of the resultant decreasing intraocular pressure can be obtained. If the readings are taken over the course of a few minutes a graph is obtained showing a uniform descending slope. The gradient of the slope (tangent) is a measure of the ease with which aqueous can be driven out of the eye through the normal drainage channels, and thus the patient with reduced aqueous outflow should show a decrease in the gradient of this slope. Readings can also be made to demonstrate increased facility of outflow after surgery or after the introduction of medical therapy. This technique has largely been abandoned clinically because of the poor repeatability of results on individual patients. Facility of outflow (or its reciprocal, outflow resistance), expressed numerically, is reduced in groups of patients with glaucoma when they are paired with a similar group of normal patients, but a knowledge of the facility of outflow is often of little value in the individual patient. The technique of tonography is not now widely used, because of the difficulty in interpretation of results.

Experimentally, tonography gradients have been shown to reverse rapidly with rapid variations in Pa_{CO_2} (fig. 2). This is presumably the result of a rapid vascular volume change within the eye, almost certainly occurring in the choroid. These changes have been shown to be independent of central venous pressure.

Measurement of ocular blood flow

Ocular blood flow is the most difficult parameter to measure when considering ocular fluid dynamics. Ophthalmic artery pressure can be estimated by using the eye itself as a sphygmomanometer. The central retinal artery can be observed ophthalmoscopically and its behaviour on changes in intraocular pressure observed. Again, manometric pressure changes are the most accurate, but some idea of systolic and diastolic pressures can be obtained by digital compression of the globe or by the application of a calibrated spring plunger (ophthalmodynamometry). The technique of ophthalmodynamometry is not widely used, in spite of the great number of instruments which have been designed to give a numerical value to the pressures within the ophthalmic artery. The technique is mainly used for comparison of one eye with the other.

Qualitative estimation of ocular blood flow may be obtained utilizing the technique of fluorescein angiography. Following an i.v. injection of 15–25% sodium fluorescein 3 ml, serial ocular fundus photography is performed. The illuminating light is a blue light produced by filtering the emission from a xenon photographic strobe through an interference filter passing a narrow band within the blue range. The resultant blue light excites the i.v. fluorescein and causes a yellow fluorescence. The retinal vessels are photographed through a second narrow band interference filter, this time selected to absorb the blue light which may be reflected from the retina and to pass only yellow fluorescent light. The fluorescein is largely protein-bound in the circulation and since retinal vessels are normally impermeable to protein, the passage of dye through the retinal vessels is visualized clearly. The choroidal circulation can often be visualized at the same time, especially in lightly pigmented races where the mass of fundus pigment does not obscure the choroid (fig. 3). Choroidal capillaries are permeable to protein and the resultant leakage of fluorescein can be visualized

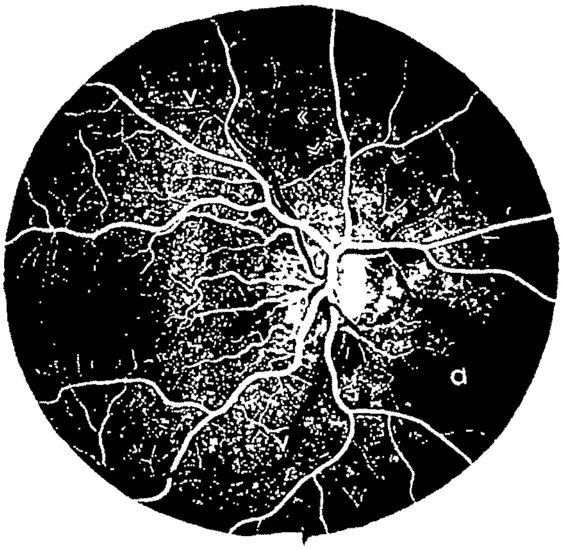

FIG. 3. A fluorescein angiogram of a normal eye. The angiogram shows dye in the central retinal artery and these vessels are brightly fluorescent. Veins show early filling and laminar flow (v). Choroidal filling from the posterior ciliary arteries is delayed in one segment and an area of the choroid remains nonfluorescent at this time (a). The water shed between the territories of two adjacent posterior ciliary arteries is seen as a dark line (chevrons).

under some circumstances. Some workers have used a technique similar to fluorescein angiography to visualize the choroidal circulation, but have used the dye indocyanine green and infra-red light in an attempt to remove the problems of obscuration by the retinal pigment epithelium.

Quantitative estimation of choroidal blood flow has been obtained by measuring the density of injected dye by the technique of reflective densitometry, by radioactive methods using injected microspheres or by inert gas clearance. The Fick principle applied to the ocular circulation can measure the clearance of radioactive xenon-133 or krypton-85 (Strang, 1976). Since there is also loss of radioactivity as a result of diffusion, the calculation of proportional loss resulting from circulation is complex. Using these methods the response of the ocular circulation under various physiological stresses has been studied and the behaviour of the normal eye can be predicted.

FACTORS CAUSING VARIATION IN INTRAOCULAR PRESSURE

In a closed elastic organ such as the eye it becomes difficult to separate the terms used to express pressure and volume. An increase in intraocular pressure is usually produced by an increase in the volume of the ocular contents and the resulting stretching of the connective tissue coat. The sclera reacts to stretching in a non-linear fashion (Gloster, Perkins and Pommier, 1957; Woo et al., 1972). Because of the presence of both collagen and elastic fibres in the sclera, the behaviour of the eye is analogous to a balloon contained within a relatively inelastic string bag. A moderate increase in volume will produce only a small increase in intraocular pressure initially, and thus a change in i.o.p. from 20 mm Hg to 30 mm Hg during an attack of acute glaucoma probably represents a moderate increase in intraocular volume. At greater pressure (70–80 mm Hg) rapid fluctuation in i.o.p. can be obtained by small changes in fluid volume because of the relative inelasticity of the now stretched sclera (Perkins and Gloster, 1957). For this reason it is easier to produce a decrease in i.o.p. at high pressures by small alterations in relative aqueous inflow or outflow.

Expression of intraocular pressure becomes meaningless once the eye has been opened surgically. The intraocular pressure is now equal to ambient pressure and has decreased because of the release of a small quantity of aqueous. During surgery, concern is not for intraocular pressure, but for the relative volume within the eye of choroid and vitreous. Loss of vitreous humour during a surgical operation was once considered disastrous. Vitreous within the anterior chamber led to rapid opacification of the cornea and blockage of the drainage angle, and vitreous within the wound led to chronic fistula formation. Contraction of vitreous subsequently led to a high frequency of traction retinal detachment. Modern surgical techniques of removal of prolapsed vitreous have greatly reduced the morbidity of vitreous loss. Prolapse of vitreous was once associated with attempted cataract extraction under general anaesthesia and a high frequency of this complication has led to a continuation of cataract surgery with retrobulbar local anaesthesia. Local anaesthesia (1% lignocaine 0.5 ml and adrenaline 1 : 200 000) to the ciliary ganglion produces a significant and measurable decrease of i.o.p. in the intact eye. Vitreous loss is caused by a relative increase in intraocular volume, when the anterior chamber is open. More accurately, it is an increase in volume posterior to the iris that causes concern. An apparent increase in volume may occur as a result of deformation of the eye by fixation sutures or the eyelid speculum and this must be guarded against by the surgeon. Occasionally, retrobulbar injection causes bleeding within the orbit and this may have a similar effect.

At the beginning of an intraocular procedure, the eye should ideally be soft before the anterior chamber is open. A sudden decompression by release of aqueous from a tense eye may produce shearing stresses on posterior ocular blood vessels and disastrous haemorrhage may occur, particularly in the atherosclerotic subject. A severe expulsive haemorrhage is rare, but may rapidly expel vitreous, retina and choroid, causing permanent blindness. Even when bleeding is not profuse, small amounts of blood or transudate may produce bloody or serous detachments of the choroid, increasing posterior intraocular volume. Anaesthesia should therefore be directed to reducing choroidal vascular congestion, as the ocular blood content is probably the easiest part of the intraocular volume to influence. The administration of acetazolamide is a traditional precursor to ophthalmic surgery, but in the subject with an initially normal i.o.p., it produces only a minimal reduction in pressure and may even increase ocular blood flow (Wilson, MacKenzie and Strang, 1976). Acetazolamide also reduces aqueous outflow (Wistrand, 1964). The reduction of choroidal congestion can be accomplished by any of the factors known to reduce vascular engorgement. Thus, reduction of Pa_{CO_2}, prevention of anoxia and reduction of systemic arterial pressure and central venous pressure will reduce the choroidal blood volume. The choroid in the cadaver is usually stated as being about 200 μm thick, but evidence from ultrasound examination in the living eye suggests that it is in fact much thicker, perhaps 500 μm at physiological values for Pa_{CO_2} and c.v.p. (Coleman and Lizzi, 1979). Coleman and colleagues (1974) suggested from ultrasonic evidence that the choroid may be up to 1 mm thick at times. Figure 4 shows an ultrasonogram of the posterior ocular wall at physiological values in a conscious patient. Using simple mathematics, we can consider the volume changes which would occur in the eye with a change in choroidal thickness; a 500-μm alteration (from say 200 μm to 700 μm) would produce an increased posterior volume of more than 0.5 ml. (This is with a normal vitreous volume of about 5 ml and assuming that the choroid covers only two-thirds of the interior of the eye.) Wide variations in intraocular volume have been shown to occur instantaneously with changes in carbon dioxide tension (Wilson and LeMay, 1974; MacDiarmid and Holloway, 1976) and some observers have recorded rapid changes in intraocular pressure occurring during anaesthesia (Dominguez et al., 1974; Dominguez, Gimenez Alvarez and Sanchez Baños, 1975). These changes are so rapid that it seems definite that some sort of vascular response is involved. There seems little doubt that rapid changes in intraocular volume are the result of rapid changes in the state of engorgement of the choroid, although these changes have not been observed directly.

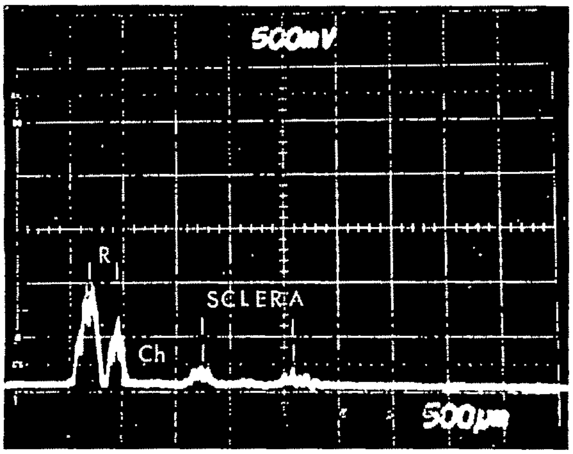

FIG. 4. A-scan ultrasound of the posterior ocular wall. The echoes produced by the retina (R) and choroid (Ch) can be seen forward of the sclera. Scale 500 μm per division (chevrons). Here the choroid is approximately 700 μm thick.

During the early stages of cataract surgery when the anterior chamber is open an increase in the volume of the ocular contents is suspected when the iris bulges or the lens spontaneously dislocates anteriorly. At this stage in the operation if time is spent attempting to reduce intraocular volume, the complication of vitreous presentation can be averted. All external deforming forces are removed. Anaesthesia should have been appropriate to the type of surgery from the initial stages of the operation, but further steps can be taken at this time to reduce ocular volume if a disaster appears imminent. The appropriate measures are discussed fully in later papers. The decreasing of systemic arterial pressure alone or the decreasing of arterial pressure and central venous pressure by an increase in the tilt of the operating table may produce a rapid decrease in ocular blood volume. I.v. sucrose (25 g of 50% solution) reduces vitreous volume, but takes 20 min to be fully effective and the increased anaesthetic time may be considered undesirable. Samuel and Beaugié (1974) remarked on the changes in i.o.p. occurring with changes in arterial P_{CO_2}. Choroidal blood flow increases with increasing Pa_{CO_2} (Strang, Wilson and Johnston, 1974; Wilson, MacKenzie and Strang, 1976). In animals, increases in choroidal blood volume accompany increases in choroidal blood flow (Bettman and Fellows, 1956). The volume of the choroid can be reduced if Pa_{CO_2} is kept small and if hypoxia is avoided. Control of these parameters, more than any others, prevents vitreous prolapse. Reduced congestion also minimizes bleeding from the wound, and reduces the risk of posterior bleeding with consequent choroidal detachment or expulsive haemorrhage. The retinal and orbital vessels respond in a similar fashion to choroidal vessels, but the contribution of engorgement of these vessels to vitreous presentation is probably slight. Certainly, haemorrhage within the orbit has to be gross before compression of vessels or an increase in i.o.p. is produced, and similar volume changes in the orbit are not likely to be produced by simple engorgement of vessels. If immediate measures have been successful the surgeon observes recession of the lens–iris diaphragm. Subsequent surgery is likely to be uncomplicated.

In the present short review, the volume of the ocular contents has been given great prominence. Little mention has been made of the additional complication of bleeding occurring during surgery.

There is no doubt that because of a reduction in bleeding generally, hypotensive anaesthesia has made developments in ophthalmic surgery possible and technical advances in surgery have paralleled advances in anaesthesia. Perhaps it is more honest to say that advances in surgery have only been possible after the appropriate improvements in anaesthesia. It is only with a full knowledge and understanding of the ocular fluid and vascular physiology during anaesthesia that we can contemplate embarking on difficult and otherwise hazardous procedures such as partial choroidal resection or dissection within the orbit. These topics are discussed by Foulds elsewhere in this issue (Foulds, 1980).

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ANAESTHESIA FOR EYE SURGERY: GENERAL CONSIDERATIONS

A. K. ADAMS AND R. M. JONES

Ophthalmic surgeons rarely deal with life-threatening problems, although the diseases may be distressing, inconvenient or disfiguring. Nevertheless, eye conditions assume great importance to the sufferer, because the threat or fear of blindness is always in the background.

Many patients presenting for eye surgery suffer from coincidental illness which makes them poor risks for anaesthesia. These include cardiovascular and respiratory diseases, diabetes and renal disorders. The infirmities of old age are such that the preservation and restoration of eyesight is of great importance, particularly to those whose horizons may be limited to their homes and their television screens.

Whilst many patients will not pose serious problems to the trained anaesthetist some, including the very young and the very old, will tax the skills of even the most experienced. Perhaps it is this aspect, coupled with the limited nature of the surgery, which makes ophthalmic practice one of the most rewarding fields in which to participate.

This paper will consider the practical problems which the anaesthetist encounters in eye surgery, and indicates various ways in which these can be overcome.

REQUIREMENTS FOR OPHTHALMIC OPERATIONS

Immobility of the eye is essential, especially as many procedures are now performed under the operating microscope.

The second requirement is that the intraocular pressure (i.o.p.) should be low for intraocular procedures, such as cataract extraction, glaucoma drainage and penetrating corneal grafts. When the eye is opened i.o.p. equals atmospheric pressure. If it is very high before opening the eye, the sudden decrease may cause serious complications such as iris prolapse, vitreous loss, retinal detachment or expulsive choroidal haemorrhage. Factors which increase i.o.p. include carbon dioxide retention, the use of suxamethonium, and high systemic venous pressure such as occurs with coughing and straining.

The dangers of the oculo-cardiac reflex must be avoided (Dewar and Wishart, 1976). Traction on the extrinsic muscles of the eye may produce bradycardia, arrhythmia or even cardiac arrest. The afferent stimulus travels in the ciliary branches of the ophthalmic division of the trigeminal nerve, and the efferent pathway to the heart is via the vagus nerve. The reflex can be interrupted by retrobulbar block with local anaesthetic or by vagal block with atropine.

In some operations it is an asset if bleeding can be minimized.

After all eye operations, recovery from anaesthesia should be peaceful, with no restlessness, coughing or vomiting.

Finally, the surgeon should be free from distraction whilst carrying out delicate work using a microscope or other lens.

These requirements must be met with the minimum risk and disturbance to the patient.

MANAGEMENT BEFORE OPERATION

As a rule, patients should be admitted to hospital the day preceding operation to allow careful routine examination. In some cases, for example patients with diabetes, admission may require to be several days before operation.

Most ophthalmic operations are non-urgent, and it is essential that patients should be as fit as possible before operation. Patients with respiratory disease should stop smoking and have preoperative chest physiotherapy to reduce sputum production and clear the airways; a sample of sputum should be cultured and the antibiotic sensitivity determined. Where respiratory function can be improved, the operation should be deferred, because severe coughing in the period after operation may compromise the result. Cardiac failure should be treated, and arterial hypertension brought under control, although over-enthusiastic treatment with antihypertensive agents is often not indicated in the elderly.

The haemoglobin concentration should be estimated in all patients except children, and serum urea

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0007-0912/80/070663-07 $01.00

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and electrolyte concentrations measured in patients with hypertension or diabetes, in the elderly and in all patients receiving digitalis or diuretics. Hypokalaemia should be corrected before operation.

Diabetes

Diabetes is now the commonest cause of blindness in adult patients in the United Kingdom. Its ocular complications are well known and their frequency increases as the disease progresses. Diabetics suffer from cataracts, vitreous haemorrhage, retinal disease and neovascular glaucoma and surgery may be required for any or all of these.

Blood glucose and electrolyte estimations and urine testing will indicate the degree of control, and operation should not be undertaken in the presence of ketonuria or excessive hyperglycaemia. Oral hypoglycaemic agents should be withheld before operation; it may be necessary to discontinue chloropropamide for 24–36 h beforehand. Blood glucose concentrations may indicate a need for doses of soluble insulin.

The management of insulin-dependent diabetics will follow usual lines, either using small doses of soluble insulin and a 5% dextrose drip, or a constant insulin–dextrose infusion. The danger of hypoglycaemia during anaesthesia and recovery must of course be avoided, but management is aided by the fact that most patients will resume a normal oral intake on the evening of operation or early the next morning.

Many patients with longstanding diabetes have renal impairment and cardiovascular complications of their disease, and the effect of these on anaesthesia must be considered.

Dystrophia myotonica

This condition is associated with the development of cataracts at a young age, and presents special risks during anaesthesia because of associated cardiac and respiratory disease, and a tendency to prolonged respiratory depression following normal doses of anaesthetic drugs. Suxamethonium should not be used in these patients because of the risk of myotonia, and if thiopentone is used, the dose should be kept to a minimum.

PREMEDICATION

There is little indication for analgesic premedication in ophthalmic surgery. Opiates and pethidine increase the risk of vomiting after operation and most operations, except those for the correction of squints and some retinal detachment procedures, cause very little discomfort after operation.

Premedication can ensure a smooth induction of anaesthesia and promote a tranquil recovery. Only sedative and antiemetic effects are needed; for simplicity and convenience the oral route is preferred. Diazepam 5–20 mg (according to age, size and general condition) is effective in dispelling anxiety, and droperidol 5–10 mg or perphenazine 4–8 mg in preventing nausea and vomiting. Some anaesthetists prefer to omit the antiemetic drug, giving it instead by injection towards the end of the operation.

Sedative premedication in children should be according to the preference of the individual anaesthetist and is dealt with in more detail elsewhere (Arthur and Dewar, 1980).

The use of antisialogogue agents is controversial. When given orally, large doses are needed to ensure drying of secretions, and this tends to produce viscid secretions which can be troublesome after operation. Atropine is used routinely, however, in small children who have very active vagal reflexes, and in whom salivation may be profuse, and is given orally or i.m. in doses up to 0.6 mg. The antiemetic and tranquillizing action of hyoscine may be of use in the younger patient undergoing surgery, but should be avoided in the elderly.

Atropine has been regarded as contraindicated in patients with narrow-angle glaucoma. Recent work by Cozanitis and others (1979) shows that standard premedicating doses given systemically have no effect on pupil size or i.o.p. in normal eyes. In patients known to have glaucoma, the instillation of 1–2 drops of 1% pilocarpine into the conjunctival sac ensures a small pupil regardless of the dose of atropine.

Some surgeons ask for an infusion of mannitol to be given in the anaesthetic room, so that increased i.o.p. may be decreased by the osmotic diuretic effect. A dose of 1–1.5 g kg^{-1} is usually given over 15–20 min, and this should be followed by a slow infusion of physiological salt solution to compensate for the diuresis. The dangers of circulatory overload in patients in cardiac or chronic renal failure must be remembered.

CHOICE OF ANAESTHESIA

There are several ways in which the requirements of safe surgery can be met, the first decision being between local and general anaesthesia.

Intraocular operations, with the exception of retinal detachment surgery, can be carried out under local analgesia, and this was the standard practice for eye surgery in the days when general anaesthesia was less reliable.

General anaesthesia ensures an immobile patient and avoids sudden cough or sneeze or a request to sit up. It frees the surgeon from constant communication with and reassurance of the patient, and gives ideal conditions for surgery by producing a soft eye with low i.o.p. However, many surgeons are experienced in the use of local analgesia and are happy to use it where the physical state of the patient indicates. The final decision, therefore, calls for good liaison before surgery between surgeon and anaesthetist.

The increased use of general anaesthesia has made surgery possible in the senile, the mentally disturbed and the deaf patient, in all of whom operating under local anaesthesia is contraindicated. Patients with chronic respiratory disease, who might be considered ideal candidates for local analgesia, may not be able to control their coughing, and general anaesthesia then becomes necessary. Most patients, if asked, would prefer to be asleep for their operation, but old people are generally phlegmatic, and procedures performed under local analgesia are tolerated well.

Local analgesia is not without complications. Adequate analgesia requires an extensive regional block including facial nerve blocks and retrobulbar injections. This latter procedure is uncomfortable, and even in expert hands may result in a retrobulbar haematoma, causing proptosis and congestion of the globe; the operation must be deferred for several weeks until the haematoma has subsided, thus making this method an unsuitable choice for urgent operations. Furthermore, local blocks do not always succeed in producing sufficient analgesia, some patients with cardiac and respiratory disease do not tolerate lying flat, and postoperative confusion may occur after this technique as well as after general anaesthesia.

General anaesthesia is becoming increasingly popular (Adams, Freedman and Henville, 1979), probably because anaesthetists have a better understanding of the needs of eye surgery. The scope of surgery is extending, and the use of the operating microscope not only gives better surgical results, but the absolute immobility required is difficult for even the most co-operative patient to maintain. Published series suggest that morbidity and mortality need not be increased significantly by general anaesthesia. In a large series, Wolf, Lynch and Berlin (1975) showed that mortality following cataract extraction under general anaesthesia was no greater than that expected in a non-hospitalized population of the same age group. Experience in our hospital confirms this. In our practice it is rare for patients to be refused general anaesthesia on medical grounds.

Perhaps the least satisfactory technique is that of local analgesia supplemented by heavy sedation. The latter is unpredictable in its effects in the elderly and may result in ventilatory depression, loss of airway control, hypotension and prolonged recovery, whilst restlessness during or after the procedure is not uncommon.

Patients with eye disease may have repeated operations, for example the second eye may be operated on a few days or weeks after the first, and this may influence the choice of anaesthetic drugs.

General anaesthesia

Many techniques have been advocated. In our hands the following meets the requirements more closely than others we have tried.

Fentanyl 1–2 μg kg^{-1} is given i.v. and 2–3 min later induction is completed with thiopentone 3–4 mg kg^{-1} and alcuronium 0.2–0.25 mg kg^{-1}. A single dose of fentanyl provides good analgesia for the average operation lasting 20–40 min. It has little adverse effect on the circulation and helps to avoid coughing when the tracheal tube is removed. Alcuronium is chosen for its rapid onset of action, relative lack of cardiovascular effects and ease of antagonism. Pancuronium may be used when arterial hypotension is especially undesirable, or where there is a possibility of hypovolaemia following intensive treatment for acute glaucoma.

The larynx and trachea are sprayed with 4% lignocaine solution and the trachea intubated. Intermittent positive pressure ventilation with nitrous oxide and oxygen is started cautiously, particularly in frail patients whose cardiac output may become dangerously reduced. Adams, Freedman and Henville (1979) have shown that, with normocarbia, i.o.p. is satisfactory for safe surgery. However, if the surgeon requests a further reduction in i.o.p., hyperventilation is a simple way of achieving this (Adams and Barnett, 1966; Samuel and Beaugié, 1974). If anaesthesia is inadequate to ensure immobility, we prefer to give a volatile anaesthetic agent rather than increase the dose of either analgesic or relaxant during these relatively short operations. Both halothane and enflurane decrease i.o.p. (Runciman et al., 1978), although they may also cause hypotension in the elderly. Trichloroethylene avoids this danger, although its effect in decreasing i.o.p. is less (Adams, Freedman and Dart, 1979). In some patients a second operation on the other eye may occur within a few days or weeks, and halothane should be avoided in these.

At the end of the operation gentle pharyngeal suction is carried out before antagonizing the neuromuscular blockade. The use of atropine–neostigmine mixtures has minimal effects on pupil size (Rawstron and Hutchinson, 1963). Straining and coughing can be minimized by gentle extubation. If a face-mask is used after extubation, care must be taken not to press on the operated eye.

We have found this technique useful for all intraocular operations, providing excellent conditions for the surgeon and a rapid, smooth recovery. It avoids the disadvantages of deep general anaesthesia with spontaneous breathing, which results in carbon dioxide retention and a much slower recovery with more chance of restlessness.

Monitoring

The heart rate should be monitored continuously throughout anaesthesia by palpation or plethysmography, and arterial pressure measured frequently. The electrocardiograph should be monitored in patients with cardiovascular disease. There must always be access to a vein by an infusion or an indwelling needle, and atropine must readily be available to block the effects of the oculo–cardiac reflex because premedicant doses of atropine may be inadequate; if profound bradycardia occurs the surgeon must be asked to wait until vagal block is effective.

POSTOPERATIVE CARE

Occasionally the surgeon will wish patients to be kept in a specified position, but usually they can be nursed on their sides breathing oxygen-enriched air until recovery is complete.

Restlessness and disorientation after operation are surprisingly uncommon, even in the oldest patients. The use of long-acting drugs in premedication ensures that patients are restful for several hours, though easily rouseable. Mental confusion may result from dehydration, and oral fluids should be started within a few hours; if they are not tolerated an i.v. infusion may be needed.

Analgesia is seldom needed after operation, except following procedures for correction of squint and retinal detachment. Vomiting must be avoided, and when an antiemetic drug is included in the premedication or given during anaesthesia it is rare, although occasionally the drug may need to be repeated after operation. Patients with bronchitis may be helped to control their coughing by the use of an antitussive linctus.

Patients are kept in bed on the day of operation but usually sit out in a chair the next day, and early ambulation is encouraged.

SPECIAL PROBLEMS

Glaucoma

Acute angle-closure glaucoma may present as a generalized disease with severe malaise, nausea, vomiting and pain which is not localized to the eye. Once the diagnosis has been made, intensive treatment with topical eye drops to decrease the ocular tension may extend over several days. This may be supplemented with the systemic use of diuretics or of acetazolamide, a carbonic anhydrase inhibitor, each of which adds to the dehydration from which the patient may already be suffering. When the patient is presented for surgery the induction of general anaesthesia may be followed by a sudden and severe decrease in cardiac output. This should be anticipated in all patients under these circumstances and an i.v. infusion be ready to correct hypovolaemia, and occasionally a small dose of a vasopressor, such as ephedrine 10–20 mg may be indicated.

Chronic simple glaucoma is a much commoner condition and presents more insidiously; there may be considerable permanent visual field loss before the patient seeks help. For many years management has been based on the use of eye drops, surgery being reserved for patients not relieved by these means. Various agents are available, including parasympathomimetics (e.g. pilocarpine), and anticholinesterases (e.g. eserine, ecothiopate), both of which cause paralysis of accommodation and miosis, and sympathomimetics (e.g. adrenaline, phenylephrine) which produce miosis without cycloplegia. Although these agents are absorbed into the systemic circulation, the only one causing serious effects is ecothiopate. The use of this powerful and long-acting anticholinesterase results, within a week or two, in a decrease in the serum pseudocholinesterase to a concentration at which prolongation of the actions of suxamethonium and procaine will occur (De Roetth et al., 1965; McGavin, 1965). Generalized cholinergic symptoms have also occurred in these circumstances and a case has been reported in which abdominal pain and diarrhoea resulted in laparotomy (Gesztes, 1966).

Medical treatment of glaucoma is unsatisfactory because of the high frequency of unpleasant side-effects from drug therapy; thus patients often do not comply with their treatment. The result is poor control of the ocular tension and if acetazolamide is then prescribed, the patient's discomfort is further increased by the diuresis and metabolic acidosis it produces. More recently, beta-adrenergic blocking agents have been used to decrease i.o.p., and these may have effects on beta receptors elsewhere in the body. The poor results of conservative management mean that increasingly this is used only as a temporary measure whilst patients are awaiting admission to hospital for trabeculectomy, iridectomy or other drainage procedures.

In anaesthetizing these patients one must be aware of their previous drug therapy, and the possible complications arising from this. The effect on i.o.p. of agents and manoeuvres used during anaesthesia must also be borne in mind, and these are described in detail elsewhere in this issue (Holloway, 1980). The glaucomatous eye does not always respond in the same way as the normal eye. It is often the case that i.o.p. increases less in response to hypertensive stimuli, but this is inconsistent and the anaesthetist should be careful to avoid agents and actions likely to increase the pressure.

It has been traditional to regard atropine as contraindicated in patients with glaucoma, but this does not apply to the systemic use of atropine in the doses needed before and during anaesthesia.

Retinal detachment operations

The patients are best managed as for intraocular procedures, particularly as the operations may be prolonged. Rotation of the globe with traction on the extraocular muscles stimulates the oculo–cardiac reflex, so i.v. atropine may be needed to block the cardiac response. Occasionally, giant retinal tears may be operated on with both the patient and the surgeon in unusual postures to allow gravity to assist in re-attaching the retina. The patient may be strapped to a special table and operated on face down, on his side, or in a steep head-up or head-down tilt according to the site of the lesion. Fortunately, these lesions occur most commonly in young patients who tolerate changes in posture reasonably well, although an i.v. infusion is a wise precaution to combat possible postural hypotension.

Extraocular operations

For squint correction the same technique may be employed, or alternatively, intubation after the administration of a short-acting neuromuscular blocking agent may be followed by spontaneous breathing with nitrous oxide and a volatile agent. Again the oculo–cardiac reflex may be active.

Ocular examination under anaesthesia

This is most likely in infants and children, for refraction, probing of lachrymal ducts or for measurement of i.o.p. in infants with glaucoma. Often the patients attend as day cases. Anaesthesia with nitrous oxide and halothane via a small face-mask is sometimes adequate, although endotracheal intubation following a muscle relaxant may be preferred. Ketamine is an alternative that may be useful, particularly in small infants because it allows unimpeded access for the surgeon without the need for tracheal intubation. I.o.p. is greater with this agent than with halothane (Adams, 1973) although possibly closer to that in the awake active child.

Plastic procedures

Extensive operations on the lids, orbit, or lachrymal apparatus are easier if bleeding can be minimized by induced arterial hypotension. The same considerations apply here as in the use of hypotensive agents for any surgical procedure. Vasoconstriction in the nasal mucous membrane before dacryocystorhinostomy is a help, and may be achieved with adrenaline-soaked gauze packs, or 25% cocaine paste; a throat pack must be inserted.

Emergency operations

Trauma to the eye, particularly penetrating injury of the globe, presents a dilemma to the anaesthetist. The patient will be unprepared and may have a full stomach. The use of suxamethonium for "crash induction" will increase i.o.p. and may possibly cause further damage to the eye by extrusion of its contents. It is often assumed that the risk of regurgitation and pulmonary aspiration is increased by the use of a more slowly acting non-depolarizing agent. Barr and Thornley (1976, 1978) have suggested that suxamethonium is not essential in the induction of anaesthesia in patients at risk of regurgitation. They compared the risks of pulmonary aspiration following thiopentone–suxamethonium and thiopentone–pancuronium inductions and found that neither invariably produced ideal intubating conditions. On balance, pancuronium was safer because it avoided the increase in intragastric pressure that occurs with suxamethonium. The administration of small doses of non-depolarizing agents before suxamethonium does not abolish the increase in i.o.p. (Bowen, McGrand and Hamilton, 1978).

Whilst a person's life must obviously not be jeopardized in favour of his eye, it does not seem necessary to use suxamethonium, unless possibly when a difficult intubation might be anticipated. Repair of an injured eye is rarely extremely urgent, and some time can be taken to lessen the hazards of regurgitation by giving metoclopramide to speed up gastric emptying, and cimetidine and antacids to reduce acidity. A naso-gastric tube must never be used to empty the stomach in the presence of an eye injury, because the retching it causes will increase the venous pressure and certainly add to the damage. Preoxygenation, fentanyl followed by thiopentone, a large dose of pancuronium and cricoid pressure until the trachea is intubated is an acceptable technique which helps to protect the eye from further damage. Fazadinium has been advocated as an alternative because of its rapid onset of action (Blackburn and Morgan, 1978) and the absence of an ocular hypertensive effect (Couch, Eltringham and Magauran, 1979).

Non-ophthalmic operations

Patients with ocular disease do of course present for other operations. Following a fracture or acute retention of urine the patient may forget about his usual therapy, and glaucoma in particular may become uncontrolled. Anaesthesia for other operations in patients with known eye disease should therefore be conducted bearing in mind the principles of ophthalmic anaesthesia.

Insufficient care is taken of patients' eyes during anaesthesia. Corneal damage, an unnecessary event, regrettably occurs from time to time. It may be a result of drying of the cornea when the eyes are not firmly closed, or to abrasions inflicted by towels, or careless turning of patients to the side, dragging the eyelids on the pillow. The eyes should be closed with non-irritant adhesive tape, and protected by eye-pads on every occasion when the eyes are not constantly in the anaesthetist's view. If damage occurs it is usually sufficient to keep the eye closed under a pad for 1–2 days for healing to occur, but the advice of an ophthalmologist should always be sought.

DRUGS USED IN THE EYE

Drugs instilled into the conjunctival sac are absorbed rapidly into the general circulation and may produce systemic effects.

Sympathomimetic agents

It is well known to ophthalmologists that the use of vasoconstrictor drugs in the eye may be followed by faintness, palpitations, pallor and sweating in susceptible patients, and severe cardiac arrhythmias have been reported (Lansche, 1966). One drop of 1% adrenaline contains about 1.4 mg, a dose which, considering the rapidity of absorption from the conjunctival sac, is potentially dangerous. These risks must be borne in mind when surgeons wish to use such drugs in anaesthetized patients, especially if halothane is being given.

Treatment of glaucoma

These drugs have already been discussed.

Steroids

Corticosteroids may be used either topically or systemically, and the anaesthetist should be aware of the possible depression of the patient's own hormone production.

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CONTROL OF THE EYE DURING GENERAL ANAESTHESIA FOR INTRAOCULAR SURGERY

K. B. HOLLOWAY

> "There are nine and sixty ways of constructing tribal lays,
> And - every - single - one - of - them - is - right."
> *Rudyard Kipling*

THE PROBLEM

Interest in general anaesthesia for intraocular surgery is relatively recent. Undoubtedly, the small area involved may be anaesthetized and immobilized by retro-ocular and facial nerve blocks performed by the ophthalmologist. Also, general anaesthesia may produce problems in the many elderly patients and especially in those with concomitant systemic disease. Further, straining, coughing and vomiting associated with general anaesthesia cause serious increases in intraocular pressure (i.o.p.) which may be disastrous.

As ophthalmology advances the operative procedures become more complex, take longer to perform and are more demanding on both the surgeon and the patient. The patient's ability to co-operate may be overstretched. Whilst local anaesthesia is satisfactory for most standard procedures in skilled hands, in the complex cases the range of techniques for controlling intraocular conditions available with general anaesthesia comes into its own.

The problem is thus the control of the intraocular contents during general anaesthesia. In most intraocular operations the surgical approach is via the anterior chamber and inevitably aqueous will be lost through the incision. If at this time i.o.p. is great, the intraocular contents move towards the incision. The iris, the lens or vitreous may prolapse either immediately or when the surgeon attempts to move the lens. With a high i.o.p. during posterior chamber surgery the vitreous may present first.

Sudden release of pressure in a hard eye may produce rupture of the short ciliary blood vessels at the back of the eye, leading to a calamitous expulsive haemorrhage (Ruiz and Salmonsen, 1976).

If the eye has already been opened i.o.p. is effectively zero, but any factor which might otherwise have increased the pressure in an intact eye may result in ntraocular contents moving towards the incision or bieing lost through it.

A closed eye will normally withstand a short increase in i.o.p. without trouble, although if extraocular surgery, for example correction of a squint, is being performed there will be more bleeding.

When glaucoma is present there may already be impairment of the blood supply to the optic nerve, and increase of i.o.p. may cause further loss of visual field and acuity.

Intraocular pressure can be measured easily and accurately in most cases, but to assume that i.o.p. is synonymous with "intraocular operating conditions" is a misleading oversimplification.

There are four variable components which may be controlled: pressure from extraocular structures, aqueous volume, choroidal volume and vitreous volume.

Measurement of these is much more difficult than measuring i.o.p., and is impossible in clinical practice. Nevertheless, an understanding of the mechanisms involved in a change of i.o.p. will greatly facilitate the production of safe operating conditions within the eye.

For example, it is possible to produce a low aqueous volume but a high choroidal blood flow. Measurement of i.o.p. might produce an apparently satisfactory reading but following corneal section, after having lost the small volume of aqueous, the ophthalmologist would be faced with a visibly bulging iris, lens and vitreous.

Anaesthetic drugs

In many early studies of the effect of anaesthetic drugs on i.o.p. the conditions in which measurements were taken were not fully standardized and the mechanisms producing the measured effect were not explained. This is understandable, since the minimum

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0007-0912/80/070671-09 $01.00

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monitoring required would include arterial and central venous pressure, heart rate, Pa_{O_2}, Pa_{CO_2} and acid–base state; the value of i.o.p. readings if these are not controlled is limited.

Many general anaesthetic agents have been shown to reduce i.o.p., nitrous oxide being a notable exception. Kornblueth and others (1959) showed that thiopentone, cyclopropane, diethyl ether and divinyl ether all caused a reduction.

Magora and Collins (1961) added chloroform, trichloroethylene and halothane to the list, and showed that the decrease in i.o.p. was proportional to the inspired concentration of the agent. They suggested that all potent inhalation anaesthetics would have a similar effect.

The mechanism is not known, but may be related to the relaxation of extraocular muscle tone and to the depression of ocular centres in the diencephalon, mid-brain and hypothalamus (Von Sallman et al., 1956).

In a carefully controlled trial of patients receiving artificial ventilation with halothane in a nitrous oxide–oxygen mixture Al-Abrak and Samuel (1974a) showed a marked reduction in i.o.p. which was closely related to halothane concentration, but independent of the decrease in arterial pressure.

In a similar study the same authors (Al-Abrak and Samuel, 1973) had shown an increase associated with an increase in central venous pressure on commencing the administration of trichloroethylene.

Adams, Freedman and Henville (1979) and Adams, Freedman and Dart (1979) have used halothane and trichloroethylene in patients who received normocapnic artificial ventilation for cataract surgery. Greater decreases in i.o.p. were produced with halothane (almost 50%) compared with trichloroethylene (14–20%). Central venous pressure was not measured.

Runciman and others (1978) compared the effects of administering MAC equivalents of enflurane and halothane and found that the decrease in i.o.p. was greater with enflurane.

Thiopentone has been shown to reduce i.o.p. in both normal and glaucomatous eyes (De Roeth and Schwarz, 1956; Joshi and Bruce, 1975).

Peuler, Glass and Arens (1975) found no effect on i.o.p. after administering ketamine to adults, and Yoshikawa and Murai (1971) showed a small increase in children. However, Ausinch and others (1976) produced a 25% reduction in i.o.p. by administering ketamine i.m. to children.

Etomidate was shown by Oji and Holdcroft (1979) to produce a marked decrease in i.o.p. even in small doses, in spite of muscle movements and pain on injection.

Opiates cause a moderate reduction in i.o.p., but many anaesthetists avoid them because of their emetic effects. It is fortunate that pain is not often a serious problem after intraocular surgery.

Pressure from extraocular structures

Lid retractors may press on the eye and cause bulging of the contents in spite of the anaesthetist's best efforts. The eyelids should be retracted with sutures, or malleable stick-on disposable retractors, arranged to pull them away from the globe. Rarely canthotomy may be necessary.

In eye surgery non-depolarizing muscle relaxants are mainly used to facilitate controlled ventilation of the lungs but these drugs will also relax the extraocular muscles, and might be expected to decrease i.o.p. Al-Abrak and Samuel (1974b) found little change in i.o.p. after pancuronium, but a marked decrease with tubocurarine, associated with circulatory effects. Pancuronium and alcuronium were both found to produce no significant change by George and others (1979).

Hartley and Fiddler (1977) used fazadinium with thiopentone to aid rapid tracheal intubation in emergency cases; there was no increase in i.o.p., a finding that has been confirmed by Couch, Eltringham and Maguaran (1979).

In intraocular surgery the selection of a non-depolarizing relaxant will depend on its speed of onset and the desired effects on the circulation.

Suxamethonium has been shown to cause an increase in i.o.p. of 7–12 mm Hg (Taylor, Mulcahy and Nightingale, 1968; Pandey, Badola and Kumar, 1972). The increase is rapid in onset, maximal in 1–2 min and with a duration of 5–6 min.

It is generally agreed that suxamethonium may be used safely if the eyeball is intact, as the i.o.p. effect will have worn off by the time an incision is made, but that it should not normally be used after the incision.

The suxamethonium-induced increase in i.o.p. is thought to be largely a result of an increase in tone of the extraocular muscles, which have at least two types of fibres: *tonic* fibres, which receive multiple innervation by small diameter nerve fibres, do not respond to single stimuli, but react to tetanic stimulation by producing a slow sustained contraction; *phasic* fibres are innervated by single large-diameter fibres, and respond to single stimuli with a rapid twitch (Wislicki, 1976, 1977).

Joshi and Bruce (1975) showed that, following induction of anaesthesia with thiopentone, which caused a decrease in i.o.p., suxamethonium 0.5 mg kg^{-1} caused an increase, while a dose of 1 mg kg^{-1} did not.

Extraocular muscles are unusually resistant to the effect of suxamethonium. Small doses, adequate to produce relaxation of other muscles, increase the tone of extraocular muscles by an effect on tension of tonic fibres. Larger doses affect tension of phasic fibres also, and produce some relaxation; this may be important in clinical practice.

The increase in muscle tension caused by suxamethonium may be abolished by pre-treatment with hexafluorenium, but this is not clinically useful (Katz, Eakins and Lord, 1968).

Attempts have been made to block the increase in i.o.p. associated with suxamethonium by pre-treatment with small amounts of non-depolarizing relaxants; pancuronium (Bowen, McGrand and Palmer, 1976), tubocurarine and gallamine (Bowen, McGrand and Hamilton, 1978) have all been tried and found ineffective.

Adams and Barnett (1966) showed that section of the extraocular muscles and canthotomy do not completely prevent the increase in i.o.p. caused by suxamethonium, and produced evidence that there is an increase in choroidal blood flow resulting in a greater blood volume in the eye which is partly responsible for the increase.

Carballo (1965) found that acetazolamide 500 mg administered i.v. before induction of anaesthesia prevented the effect of suxamethonium on i.o.p.

If the increase is entirely an effect on the muscles it would be difficult to suggest a mechanism for the protective effect of acetazolamide, which is normally administered to reduce the production of aqueous humour. However, Wilson, Strang and MacKenzie demonstrated in primates that i.v. acetazolamide produced an increase in choroidal blood flow to two or three times the normal value, lasting 50 min.

Thus acetazolamide may merely mask that part of the suxamethonium-induced increase in i.o.p. which is a result of choroidal vasodilatation, by pre-dilating it.

Choroidal volume

The choroid consists largely of blood vessels and the volume of blood contained within them may vary widely. This variation may be caused either by the state of vasoconstriction or vasodilatation of the choroid itself, or by distant factors such as changes in intrathoracic pressure affecting venous drainage. As choroidal blood volume is not readily measurable, choroidal thickness and i.o.p. are used as indicators.

Changes in arterial pressure have little effect on i.o.p. within the physiological range. A sudden increase in arterial pressure causes a small increase in i.o.p. because of a slight increase in choroidal volume. In an eye with normal drainage i.o.p. returns rapidly to normal even if the arterial hypertension is sustained, because of loss of aqueous, but the eye would be unpleasant to operate on.

Moderate decreases in arterial pressure also have little effect on i.o.p., but at values of systolic pressure less than 85–90 mm Hg marked reductions in i.o.p. occur (Adams and Barnett, 1966; Schroeder and Linssen, 1972). At systolic pressures of 50–60 mm Hg i.o.p. rapidly approaches zero. The reduction in i.o.p. is partly the result of a decrease in the choroidal blood volume, but also probably of failure of aqueous production. Controlled arterial hypotension is the most effective method of producing and maintaining a very small i.o.p. (in the region of 0–3 mm Hg) should it prove necessary.

An increase of central venous pressure has a far more serious effect on i.o.p. than have increases in arterial pressure. Obstruction of central venous return may be caused by coughing, straining on a tracheal tube, vomiting or a Valsalva manoeuvre. This causes an immediate increase in choroidal blood volume. If the globe is intact there will be an additional slower effect as aqueous outflow is reduced by back pressure on the veins which drain the canal of Schlemm.

A cough can produce an i.o.p. of 40 mm Hg or more. This will return to normal 30 s after the cause of the increase has ceased, but if the eye is open damage may already have occurred.

The choroidal blood flow, like the cerebral circulation, is dependent on arterial $P\text{CO}_2$. Wilson, Strang and MacKenzie (1977) measured choroidal blood flow in primates by the xenon-133 clearance technique and found a linear increase in flow of 0.5% per kPa increase of Pa_{CO_2} from 4.5 to 9.1 kPa.

Increasing the arterial $P\text{CO}_2$ has been shown to cause an increase of i.o.p. (Samuel and Beaugié, 1974; Wilson et al., 1974), while a reduction below normal causes a decrease (MacDiarmid and Holloway, 1976).

The increase in choroidal blood flow following i.v. amiphenazole has already been mentioned.

The choroidal circulation is affected by arterial $P\text{O}_2$. Saltzman and others (1965) studied the effects of breathing oxygen at pressures of 1–3.7 atmospheres absolute. Profound choroidal vasoconstriction, which correlated with the increase in Pa_{O_2} occurred within 3 min. The vasoconstriction was much more marked than that associated with hyperventilation, but reversed in 1 min on breathing air. This effect does not appear to have been used to facilitate intraocular surgery, presumably because of the scarcity of hyperbaric operating facilities or the inconvenience of using them.

Vitreous volume

The vitreous is an unstable gel with a fine fibrillar supporting structure and consisting mainly of water. The inert appearance is deceptive, there being a continuous turnover of the water content.

Acute angle closure glaucoma can be extremely painful and distressing, but rapid relief may be obtained by dehydrating the vitreous. Initially, urea was used for this purpose, 1–2 g/kg body weight given i.v. as a 30% solution in water. It is very effective in decreasing i.o.p. but because many of the patients are elderly with co-existing hypertension or renal disease, it has largely been superseded by mannitol.

Mannitol is given in doses of up to 1.5 g kg^{-1} as an i.v. infusion of 20% solution and will produce relief within 40 min lasting a few hours. It may then be decided to proceed with a surgical drainage procedure and the anaesthetist will be presented with a rather dehydrated patient who is experiencing a marked diuresis and who will require urethral catheterization if rendered unconscious.

The oral administration of glycerol up to 2 g kg^{-1} may be used either alone or to enhance the effect of mannitol on the vitreous volume. If a patient with acute glaucoma is presented for general anaesthesia, this should always be enquired about because of the risk of regurgitation.

If mannitol is used to reduce i.o.p. for elective intraocular surgery under anaesthesia, administration should commence 45 min before operation and the patient must be catheterized when unconscious; this may be a disadvantage, particularly in elderly men who may be developing prostatic obstruction of the urethra.

A more rapid response can be obtained by an i.v. bolus injection of 1 g kg^{-1} of a 50% aqueous solution of sucrose. I.o.p. will decrease significantly in 5 min, accompanied by an increase in arterial pressure and heart rate. Thus the effect is rapid enough to be of use if the eye is tense during the surgical procedure, but it is essential first to determine the underlying cause of the trouble.

Diuresis is not a problem with sucrose and routine bladder catheterization is not necessary.

MANAGEMENT OF PATIENTS UNDERGOING INTRAOCULAR SURGERY

With so many ways of influencing i.o.p. available to the anaesthetist, it is not surprising that a variety of anaesthetic techniques has been employed for intraocular surgery. If the method used is based on an understanding of the mechanisms of i.o.p. changes a satisfactory result is likely, and in difficult cases the anaesthetist may take some of the credit for the success of the operation.

Conversely, if the anaesthetic management is unsatisfactory, this will be apparent to the surgeon and some responsibility for operative complications must be taken.

The same anaesthetic technique will not be appropriate for all intraocular cases. The writer works in a unit where a high proportion of the patients are secondary referrals from other ophthalmologists, and encounters a wide range of difficulties presented and of the amount of control of intraocular conditions required. The use of a standard technique for all cases would result in some patients receiving an unnecessarily severe physiological insult, or some eyes being at risk, or both. It is no longer true to say "when an eye is to be opened the intraocular pressure should be as low as possible" (Duncalf and Rhodes, 1963), since what is possible may be excessively drastic. The method of anaesthesia also must be adapted to match the age and general physical state of the patient.

Intracapsular extraction of a cataract may be taken as the typical intraocular operation in which a large opening is made in the eye.

The basic essential for all intraocular surgery is a meticulously smooth, flawless anaesthetic technique, with avoidance of coughing, straining or vomiting and adequate and unimpeded ventilation of the lungs.

Most patients with uncomplicated cataract may be anaesthetized quite simply using spontaneous ventilation with halothane. Premedication should not include drugs likely to produce ventilatory depression or vomiting. Promethazine and atropine, or diazepam and atropine, perhaps combined with droperidol in the more robust patients, are satisfactory.

The decrease in i.o.p. following thiopentone induction may compensate for the increase caused by suxamethonium, and a large dose of the latter drug may produce less of an increase than a small one (Joshi and Bruce, 1975).

Spraying the pharynx, larynx and trachea with 4% lignocaine may help to minimize the increase in i.o.p. which often accompanies tracheal intubation. The tracheal tube should be well lubricated with 5% lignocaine ointment; if there is any doubt about the tube being too long it should be shortened to avoid irritating the carina. If bronchial suction is necessary, this should be done very gently at this stage, remembering that it will not be possible to do this during the operation without inconvenience to the operating team and risk to the eye. The level of anaesthesia should then be deepened with halothane and nitrous oxide in at least 35% oxygen as rapidly as the patient will tolerate.

To maintain a low venous pressure, the operating table should be placed in 10–15° foot-down tilt, and if the expiratory valve has a resistance of more than 1 cm H_2O fully open, the spring should be shortened.

An adequate depth of anaesthesia is essential, not only to prevent any patient reaction, but also because the effect of halothane on i.o.p. is proportional to dose (Al-Abrak and Samuel, 1974a). Initial halothane concentrations of 2–5% will usually be necessary and in most cases at least 1.5% will be needed until the lens has been extracted and the first suture tied. A controllable reduction in arterial pressure may be considered desirable in many cases, but excessive circulatory depression is a risk in frailer patients if the anaesthetist is not vigilant.

Rapid breathing may cause movement of the operating field under the microscope, and may be controlled by titration with pentazocine i.v., care being taken to avoid significant ventilatory depression.

It used to be the practice of the writer to maintain deep anaesthesia until after extubation to prevent coughing at this time, with resultant strain on the suture line and the risk of iris prolapse or worse. This is no longer done, because although the patient does not cough immediately he is likely to do so within a short time. The view is now taken that, with microtechnique, a "soft" eye and plenty of time for suturing, the surgeon must be responsible for making the eye watertight.

The technique described above is unlikely to provide satisfactory operating conditions if there is any impairment of the efficiency of spontaneous ventilation as a result of respiratory disease, obesity or skeletal malformation. For such cases the technique of controlled ventilation with 0.5% halothane described by Adams, Freedman and Henville (1979) would be satisfactory. These authors used normocapnic ventilation to avoid circulatory depression during anaesthesia and postoperative hypoventilation. Gallamine was chosen for myoneural blockade because of its short action and relative lack of side-effects. Pancuronium or alcuronium could be used instead (George et al., 1979).

Satisfactory small values of i.o.p. were obtained for standard intercapsular cataract extraction. When trichloroethylene was substituted for halothane, the resulting i.o.p. decrease was less (Adams, Freedman and Dart, 1979). For most elderly patients with uncomplicated cataract this technique will soften the eye sufficiently for a safe lens extraction.

If the iris and lens bulge forward after the eye is opened, there is usually a simple explanation, such as difficulty with ventilation, straining on the tracheal tube, too light anaesthesia, pressure on the neck, or pressure on the eye from retractors. If no such cause is found, administration of 50% sucrose i.v. will shrink the vitreous and control bulging within a few minutes. The effect will last long enough to allow lens extraction and insertion of corneal sutures in safety.

Cataract extraction may be made more hazardous by various complicating factors. In younger patients the attachments of the lens to the zonule are stronger and it may also be adherent to the vitreous face. Patients with diabetes mellitus often have a weak lens capsule which ruptures more easily, a pupil which will not dilate adequately and vitreous which degenerates, becoming more watery and thus more easily lost.

Vitreous degeneration may also follow uveitis or trauma, and often accompanies myopia. Adhesions within the eye may occur after uveitis, trauma or previous detachment or other operation.

There may be co-existing glaucoma, and it is becoming more common to perform combined operations, such as cataract extraction accompanied by trabeculectomy.

Preoperative dislocation of the lens is particularly troublesome if it is posterior and there is vitreous in front of it. This can occur simply as a complication of cataract, or part of the syndrome in homocysteinuria or Marfan's disease.

If the patient has only one saveable eye this is an added burden of responsibility upon the operating team, even in the absence of other complications. In many of these cases the risk to the eye will be less if a greater degree of control of intraocular conditions is used than has so far been described. Since this will involve greater physiological disturbance, the degree of assistance required from the anaesthetist should be discussed with the surgeon. It is fortunate that most of the more difficult problems occur in the younger patients.

Hyperventilation of the lungs is relatively safe and the resulting choroidal vasoconstriction reduces the i.o.p. and decreases bleeding. Excessive hyperventilation is not necessary and may cause a troublesome increase in central venous pressure. Pa_{CO_2} 4 kPa or slightly less should be aimed at, and may be conveniently monitored with an end-tidal carbon dioxide sampler. Central venous pressure is controlled by a foot-down tilt of 10–15°, a short but not abrupt inspiratory phase from the ventilator, and the use of a negative end-expiratory phase of -10 cm H_2O.

The disadvantages of this pattern of ventilation, such as intrapulmonary gas trapping, and increased shunt must be recognized, but significant upset is rare in practice.

Where necessary, for example when several complications occur together in the same eye, intraocular conditions may be further improved by substituting tubocurarine for gallamine, pancuronium or alcuronium, and by increasing the concentration of halothane administered (Al-Abrak and Samuel, 1974a, b). The combination of a high tissue concentration of halothane, hypocapnoea and circulatory depression will produce a very soft eye. To view an apparently easy and uncomplicated cataract extraction in a young diabetic person with myopia and glaucoma in the only functioning eye, is rewarding.

The increase in choroidal blood flow following i.v. acetazolamide has been mentioned and this should not be used as a preoperative measure to decrease the i.o.p. in cataract surgery complicated by glaucoma. Reducing the quantity of aqueous in the anterior chamber may make the initial incision safer, but thereafter the bulging choroid may push the intraocular contents forward. In these circumstances sucrose may be unsatisfactory and the best way to control the eye is to initiate controlled arterial hypotension with trimetaphan or sodium nitroprusside.

If intracapsular cataract extraction is to be followed by the insertion of a lens implant, it is important that the anterior vitreous face should be well back and unbroken. There is a good case for adding the preoperative administration of mannitol to a hyperventilation technique. The need for bladder catheterization may be acceptable when a compact vitreous with a well-defined and receding face is produced.

Many intraocular operations are performed in which the incision of the globe is very small, and there is not the same risk of extrusion of intraocular contents, particularly vitreous, as occurs in intracapsular cataract extraction. These include the drainage procedures for the treatment of glaucoma, such as peripheral iridectomy, iridencleisis and trabeculectomy, and a growing list of others, such as needling, phako-emulsification and vitrectomy. The risk of sudden decompression of a hard eye is still present and it may be difficult or impossible to perform a satisfactory drainage procedure if the iris is protruding into the incision.

Although very small values of i.o.p. are not necessary, the anaesthetic requirements for these cases are the same as those for cataract extraction and similar techniques can be used. Replacement of the cornea with a full thickness graft also requires control of i.o.p. but this must not be excessive. If the eye is made too soft, accurate suturing of the graft becomes more difficult.

Retinal detachment surgery is "extraocular", but a reduction in i.o.p. makes the application of indenting plombs and bands easier and the release of subretinal fluid safer. It is also associated with less bleeding.

Ophthalmoscopy at the end of a detachment procedure sometimes reveals that an equatorial band has been applied too tightly. The retinal reflex is pale and the blood supply to the eye is jeopardized. It is usual to remove the band and replace it, which is a time-consuming procedure and risks that the band will be too loose. If aqueous drainage is adequate and the ophthalmologist agrees, this problem can be managed differently by giving 50% sucrose i.v. The simultaneous decrease in i.o.p. and increase in arterial pressure so produced will restore the blood flow through the eye; by the time sucrose effect has worn off the eye will have adjusted its own internal volumes.

Intraocular tumours

Until recently an intraocular tumour has been an indication for removal of the eye unless the condition could be treated by radiotherapy. Excision of the tumour with preservation of the eye is often possible now and the writer has anaesthetized 40 patients for this procedure. Their age has ranged from 23 to 74 yr, but most have been nearer the young end of the scale, only two being older than 60 yr.

The most demanding cases are patients with choroidal melanoma since the surgery is delicate and prolonged and the tumour is extremely vascular. After incising the conjunctiva and detaching appropriate extraocular muscles from the globe, a square flap of the outer layers of the sclera over the tumour is turned back. The inner layer of sclera is then excised, complete with the tumour. This involves cutting through the choroid all round the tumour, and during this the bleeding must be controlled. The outer layer of sclera is then replaced and sutured in position, or if it is invaded by tumour a scleral graft from a donor eye is applied.

The procedure takes from 2 to 4 h and for much of this time there is a large hole in the posterior chamber of the eye. I.o.p. must be as small as possible, but achieving this may be made more difficult because the tumour mass takes up a significant part of the intraocular volume. Controlled hypotension is used to control both i.o.p. and bleeding.

The anaesthetic technique is as for a difficult cataract operation. Hyoscine replaces atropine in the premedication to try to maintain a slower heart rate. Anaesthesia is induced with thiopentone, the trachea is intubated after injection of tubocurarine and the lungs hyperventilated with 0.5% halothane in 50% nitrous oxide in oxygen with a negative expiratory phase of -10 cm H_2O; the patient is placed in the foot-down position.

While the patient's condition is becoming stable, the preliminary precise mapping of the tumour is carried out, and arterial hypotension is induced when the operation proper commences. Because the operation is lengthy and fluctuations in arterial pressure must be avoided, short acting hypotensive agents are not used, hexamethonium bromide being preferred. If tachycardia more than 90 beat min^{-1} occurs an attempt is made to control it with propanolol i.v. It is advantageous to produce the ultimate part of the arterial pressure reduction with halothane, and if high concentrations are needed, as is the case in the young and fit, they are given.

A systolic arterial pressure of 50–55 mg Hg is maintained for the early part of the operation and this combined with the anaesthetic technique used produces an eye with little or no i.o.p.

During the period of 20–30 min when the choroid is being cut and the tumour pulled from the vitreous a systolic pressure of 45–50 mm Hg is the objective; this is produced by increasing the halothane concentration. In elderly patients pressures 10 mm Hg greater will be adequate.

Although the pulsation of the central artery of the retina can be seen through the vitreous after the tumour has been excised, there will be almost no bleeding from the choroid when it is cut, and this is essential to the operation. Meticulous monitoring of the patient's cardiovascular state is essential and the author places greater emphasis on evidence of good peripheral perfusion than on pressure measurement. After the tumour has been removed and scleral suturing has commenced the inspired halothane concentration is decreased or discontinued and the arterial pressure allowed to increase slowly. Since closure takes some time it will rarely be necessary to take any active steps to restore the arterial pressure to normal.

Tumours of the ciliary body are much less vascular than those of the choroid and the smallest values of arterial pressure described above will not be needed. Tumours of the iris can usually be managed in the same way as a difficult cataract operation.

The results in terms of eradicating the tumour while preserving sight have been very worthwhile, and the experience gained is allowing larger tumours to be excised than was at first thought possible.

Penetrating eye injuries

Penetrating eye injuries cause particular concern to the anaesthetist since, added to the problem of anaesthetizing a patient whose stomach may not be empty, there is the risk that anything which increases i.o.p. may result in extrusion of ocular contents and loss of sight.

Procedures used in other emergency cases have serious disadvantages. Emptying the stomach by gastric tube is obviously contraindicated because of the straining and spluttering inevitably caused.

Suxamethonium is an essential part of the usual "crash" induction technique, but will have an effect on i.o.p. Cricoid pressure applied to prevent regurgitation may well block the venous drainage of the eye.

Other injuries, perhaps of a more life-threatening kind may co-exist, and a balanced judgement of priorities will have to be made. With regard to the eye, a smooth induction of anaesthesia and intubation of the trachea are the essentials. Thereafter maintenance of anaesthesia can be by any technique normally used for elective intraocular surgery.

The suggestion is often heard that it would be satisfactory to employ an inhalation induction with halothane, enflurane or cyclopropane, deepening the anaesthesia to allow insertion of the tracheal tube. This may be possible sometimes, but experience suggests that the depth of anaesthesia required can easily be mistaken, and this technique is not recommended to an inexperienced anaesthetist in such a case. Furthermore, if the patient does cough or regurgitate the resulting increase in i.o.p. is likely to be far greater than that produced by suxamethonium, and may also last longer.

Thus it is wiser, especially if other indications for a rapid induction are present, to use suxamethonium, using a large dose after a thiopentone induction to minimize the increase in i.o.p.

The writer prefers to use one of the more rapidly acting non-depolarizing relaxants. Fazadinium is suitable and alcuronium and pancuronium are only slightly less rapid. If the patient is able he is asked to preoxygenate himself for 5 min, since he is less likely to press the mask on his own eye. An indwelling needle is placed and, after atropine, a generous paralysing dose of the relaxant is injected. As the arm holding the mask begins to weaken, it is gently removed by an assistant as a small dose of thiopentone is rapidly injected. After a short pause smooth tracheal intubation can be performed and the patient ventilated in the usual way. This method should not be used if intubation is likely to be very difficult.

Patients with eye conditions such as glaucoma or detachment of the retina frequently require repeated surgical procedures at short intervals and the problem of repeated halothane anaesthesia will arise.

Halothane is such a useful aid in intraocular surgery that this is a serious drawback and possible alternatives also have disadvantages.

Trichloroethylene is much less satisfactory because it is associated with tachypnoea, cardiac arrhythmia and, in some cases, prolonged recovery.

Enflurane can often be an effective substitute, but the manufacturers are unsure about the possibility of cross-sensitivity with halothane or other halogenated hydrocarbons. The central nervous stimulating effect of enflurane is a contraindication to the use of hyperventilation.

Neuromuscular block-controlled paralysis, ventilation and the supplementation of nitrous oxide and oxygen mixtures with a narcotic and neurolept-analgesia are a possible alternative to halothane, although difficulties may occur in elderly patients in whom metabolism and excretion of depressant drugs may be depressed. Development of reliable methods of measuring anaesthetic depth would help with these techniques, but in complicated cases hyperventilation and hypotension are more likely to be needed.

The writer's present practice is to use halothane for all cases for intraocular surgery where management is likely to present more problems than usual, whether or not it has previously been administered. No doubt sufficient information will eventually be available to justify or condemn this practice.

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ANAESTHESIA FOR EYE SURGERY IN CHILDREN

D. S. ARTHUR AND K. M. S. DEWAR

The principles of paediatric and neonatal anaesthesia have been reviewed recently (Goudsouzian and Ryan, 1976; Vivori and Bush, 1977). It is our intention to examine those aspects most relevant to the care of patients during ophthalmic surgery or examination.

Ophthalmologists emphasize the importance of early diagnosis and correction of ocular abnormalities. Hubel and Weisel (1962) found, in the cat, that unless a clear image is focused on the retina before the age of 3 months, there was only limited anatomical and functional development of the neural connections to the visual cortex, leading to the absence of binocular vision. The longer the delay, the poorer was the visual acuity. Wybar and Taylor (1977) have shown that the same is true for man. It has also been demonstrated that restoration of binocular vision requires early correction of strabismus (Taylor, 1972). As a result, younger patients, including neonates, will require anaesthesia.

TABLE I. *Elective ophthalmic procedures requiring general anaesthesia at the Royal Hospital for Sick Children, Glasgow, 1976–79*

Operation or disease	No.	% of total	Younger than 1 yr	%
Strabismus	462	57.2	34	7.4
Examination under anaesthesia (+contact lens moulding and fitting)	154	19.1	83	53.9
Cyst (Chalazion, granulomata, dermoid)	64	7.9	8	12.5
Probing of tear duct	42	5.2	16	38.1
Cataract	23	2.8	18	78.3
Eye lid surgery (ptosis and tarsorrhaphy)	20	2.5	4	20.0
Dacryocystorhinostomy	12	1.5	2	16.7
Glaucoma	6	0.7	5	83.3
Miscellaneous (subconjunctival injections, foreign body etc.)	25	3.1	2	8.0
Total	808		97	12.0

Conditions most likely to require urgent surgery early in life are cataract and congenital glaucoma. Strabismus correction, undoubtedly the most frequent procedure (table I) is not usually performed until the child is about 2 or 3 years old as earlier detection is difficult and conservative management is often attempted initially.

Occasionally, topical anaesthesia may be used in the older, co-operative child for the measurement of intraocular pressure, but there is usually no other indication for the use of local anaesthesia in paediatric ophthalmology. Because of an inability to co-operate, many children will require general anaesthesia for non-painful procedures such as refraction and examination with the slit-lamp microscope, and indirect ophthalmoscopy which may include forcible manipulation of the eye.

PREOPERATIVE CONSIDERATIONS

There are many syndromes described in paediatric medicine involving the eye which may necessitate examination or surgery under anaesthesia. Pelton (1979) has reviewed the anaesthetic significance of many of the eponymous syndromes.

The more important conditions include Down's syndrome, which is associated with epicanthic folds and strabismus, and the rubella syndrome, with which there is a high frequency of cataract. Both conditions are associated with cardiac abnormalities and an increased sensitivity of the heart and the eye to atropine (Harris and Goodman, 1968).

Homocystinuria leads to ocular defects and is associated with intravascular thrombosis; its management has been discussed by Grover, Malhotra and Kaushik (1979). Lowe's syndrome is invariably associated with glaucoma and cataracts (Richards et al., 1965). The patients have renal impairment leading to possible electrolyte disturbances and problems with the excretion of drugs. Myotonic dystrophy is associated with cataract and ptosis, and patients with this disorder have an increased tendency to respiratory failure after operation; suxamethonium

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0007-0912/80/070681-08 $01.00

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will induce myotonia. Stevens–Johnson syndrome produces ocular erosions, and anaesthetic manoeuvres may cause bullous lesions similar to those occurring in epidermolysis bullosa. Malignant hyperpyrexia appears to be of particular importance in ophthalmology and occurs with increased frequency in the young (1 in 15 000) when compared with adults (1 in 50 000) (Britt and Kalow, 1970). The syndrome has been associated with frank myopathy and also with musculo-skeletal disorders such as kyphoscoliosis and in ophthalmic practice, strabismus (Relton et al., 1966; Thut and Davenport, 1966; Relton, Britt and Steward, 1973; Wingard, 1977) and ptosis (Hogg and Renwick, 1966); however, no specific abnormality has been detected in these patients to account for this. Many of these syndromes are familial and it is particularly important that the anaesthetist has an opportunity to interview the patient's parents before the operation.

Upper respiratory tract infection is relatively common in children and constitutes a contraindication to all but the most urgent surgery as it may increase the risk of laryngeal stridor and spasm in the period immediately after operation. The cause of pyrexia should be sought and treated and elective surgery should be postponed for therapy. Ecothiopate iodide may be used in the treatment of glaucoma and as this drug causes a reduction in the activity of serum cholinesterase, the action of suxamethonium may be prolonged (Pantuck, 1966).

PREPARATION BEFORE OPERATION

It is unusual for patients requiring elective eye surgery to require the correction of fluid depletion or electrolyte imbalance. However, children, in particular those less than 4 years old, may develop metabolic acidosis as a result of preoperative starvation and hypoglycaemia (Bevan and Burn, 1973; Editorial, 1974; Morrice et al., 1974; Thomas, 1974). It is important to reduce the duration of fasting to a minimum; infants may ingest clear fluid until 4 h before surgery, but should not be given milk during the 6-h period before anaesthesia. Older children should be fasted from midnight for a morning operation and should be allowed to have a light breakfast before an afternoon operation.

The vast literature on preoperative drug therapy for paediatric anaesthesia demonstrates that there is no single suitable method. We consider that children less than 1 year of age should not receive pharmacological sedation and will benefit more from careful and gentle handling. Children aged 1–5 yr are often difficult to console and may not understand the enforced separation from parents and home. They may benefit from profound sedation so that they arrive asleep in the operating room. I.m. injections are unpopular with patients and nursing staff alike and are rarely, if ever, required before ophthalmic surgery. We have found diazepam 0.2–0.4 mg kg^{-1} given orally with droperidol 0.2 mg kg^{-1} to be very satisfactory. The antiemetic effect of droperidol is long-lasting and powerful (Edmonds-Seal and Prys-Roberts, 1970) and is useful following the types of surgery in which vomiting should be avoided, such as intraocular procedures. Studies by Meyers and Muravchick (1977) have shown that the psychological trauma inflicted by the asleep induction technique is not as great as was thought previously. Whilst some have considered that the child should be allowed to cry when he feels threatened, crying and struggling cause venous congestion and an increase in intraocular pressure which should be avoided if possible. In children of more than 5 years of age, a reasoned explanation in association with mild sedation is often adequate.

Although their routine use in adult practice is declining, the belladonna alkaloids are important in paediatric anaesthesia and in ophthalmic practice in particular. Bradycardia in association with halothane, suxamethonium or laryngoscopic manipulation of the posterior surface of the epiglottis, is common in children. In ophthalmology, the oculocardiac reflex is of great importance, and is discussed later. Hyoscine can cause excitement in the very young as in the elderly (Eckenhoff, Kneale and Dripps, 1961) and is less effective than atropine in the prevention of the oculocardiac reflex. Oral preparations of both atropine and hyoscine are available, but absorption is unpredictable, particularly in the young. The drug of choice is atropine 0.015–0.02 mg kg^{-1} administered i.v. at the time of induction of anaesthesia, or immediately afterwards. Patients with Down's syndrome and rubella syndrome are sensitive to atropine, and the dose should be reduced by half (Harris and Goodman, 1968). In contrast to its topical effect, atropine administered parenterally does not have a deleterious effect in patients suffering from glaucoma, and its use should be regarded as obligatory before surgery for glaucoma in children.

THE OCULOCARDIAC REFLEX

Traction on the extraocular muscles, the application of pressure to the eyeball, or even in the absence of the globe, a tense orbital haematoma, may cause a reduction in heart rate. Afferent impulses travel in the ciliary nerves and are conducted via the ophthalmic division of the trigeminal nerve to the Gasserian ganglion and thence to the main sensory nucleus of the trigeminal nerve; the efferent pathway is vagal. Although it may occur during a variety of ocular procedures in patients of all ages, the effects are most commonly observed during strabismus surgery. In particular, it is likely to be associated with surgical manipulation of the medial rectus muscle (Bosomworth, Ziegler and Jacoby, 1958; Welhaf and Johnson, 1965; Apt, Isenberg and Gaffney, 1973). The cardiac arrhythmias associated with the reflex have been described by Alexander (1975).

Several techniques have been used in an attempt to reduce the frequency of the reflex response. Retrobulbar block using lignocaine has been shown to be ineffective (Bosomworth, Ziegler and Jacoby, 1958), as has the use of atropine administered i.m. before surgery (Alexander, 1975). Gallamine, given i.v. at the time of induction of anaesthesia, has been shown to be effective in reducing the frequency of the reflex response (Deacock and Oxer, 1962), but it is less efficient than i.v. atropine used in the same manner (Dewar and Wishart, 1976). However, atropine, although abolishing the reflex response, is associated with the development of cardiac arrhythmia. Detection of the bradycardia requires continuous e.c.g. monitoring and treatment should comprise the temporary cessation of surgical manipulation and the i.v. administration of atropine.

MANAGEMENT DURING OPERATION

General considerations

Almost all children undergoing eye surgery require general anaesthesia and the anaesthetist must provide conditions which are safe for the patient and of assistance to the surgeon. The airway must always be secured in a manner which allows the surgeon clear access to the eye. For all major operations, and for prolonged procedures, tracheal intubation will be required. Care should be exercised to prevent movements of the eye, bleeding should be minimal and the patient should be protected from the effects of the oculocardiac reflex. The control of intraocular pressure is discussed elsewhere in this issue (Holloway, 1980).

Tracheal intubation following an inhalation induction of anaesthesia frequently leads to coughing and breath-holding, which may cause an increase in intraocular pressure; it is preferable, therefore, to use a neuromuscular blocking drug to facilitate tracheal intubation. Suxamethonium produces a brief but marked increase in intraocular tension (Adams and Barnett, 1966) which is not prevented by the prior administration of a non-depolarizing agent such as tubocurarine or pancuronium (Bowen, McGrand and Palmer, 1976). Although suxamethonium appears to exert less pressor effect in the glaucomatous eye (Adams and Barnett, 1966), its use is not recommended in the presence of glaucoma. In children, the rapidity of onset of action of non-depolarizing neuromuscular blocking drugs renders them suitable for use before tracheal intubation. Pancuronium causes tachycardia and an increase in arterial pressure in children (Nightingale and Bush, 1973) which will tend to increase intraocular pressure. Tubocurarine is the drug of choice as it does not cause hypotension in children as frequently as in adults: a dose of 0.5 mg kg^{-1} should be reduced to 0.3 mg kg^{-1} in the early neonatal period as the neonate may show sensitivity to tubocurarine in the first 14 days of life (Bush and Stead, 1962). The use of topical lignocaine in the larynx is not recommended for procedures of moderate duration in children. Far from preventing postoperative coughing and sore throat, it appears that the frequency of both may be increased (Cheatle, 1965). In addition, its use will delay oral fluid intake.

The increased resistance to spontaneous ventilation resulting from the use of small endotracheal tubes and connectors (Brown, 1971; Hatch, 1978) may impose an unjustifiable increase in the work of breathing and further increase the tendency to airway closure already present in children less than 6 years of age (Mansell, Bryan and Levison, 1972). Therefore, in infants and neonates ventilation should be controlled in a manner which will enable functional residual capacity to be maintained at or more than closing volume and short, rapid ventilation is recommended. Children weighing between 10 and 20 kg can be allowed to breathe spontaneously through a tracheal tube for short periods (less than 30 min) provided that pulmonary function was normal before operation and that there is no evidence of ventilatory inadequacy during the procedure. The T-piece system originally used by Ayre (1937) and later developed by Rees (1950) is the most suitable system for anaesthesia in children weighing less than 20 kg. The function of the system has been examined extensively and appropriate gas flows calculated for both spontaneous and controlled ventilation (Mapleson, 1954; Nightingale, Richards and Glass, 1965;

Fisk, 1973; Rose, Byrick and Froese, 1978; Rose and Froese, 1979).

The control of bleeding can be valuable in certain procedures such as eyelid surgery and dacrocystorhinostomy. To achieve this, a technique of induced hypotension may be used; hypotensive anaesthesia will also reduce intraocular tension, but as a routine technique it is not recommended in children. Many hypotensive agents have been used in paediatric practice, including ganglionic blockade using pentolinium (Salem et al., 1974) and trimetaphan (Anderson, 1955) and, more usefully, sodium nitroprusside (Bennet and Abbot, 1977). Tachycardia frequently occurs in young patients in association with hypotensive anaesthesia and a beta-adrenergic blocking drug such as propranolol may be required.

The treatment of glaucoma, cataract and retinoblastoma involves continuous assessment and may require repeated anaesthesia over a prolonged period. In spite of impressive case reports (Solosko, Frissell and Smith, 1972; Carney and Van Dyke, 1972), the extent to which repeated exposure to halothane constitutes a risk in the child is not known; the possibility of creating problems for anaesthesia in adult life must also be considered. Enflurane is an alternative and some favour its use in paediatric anaesthesia (Govaerts and Sanders, 1975). However, Steward (1977) did not detect any advantage for enflurane when compared with halothane in children. Induction does not appear to be more rapid with enflurane than with halothane. MAC values of volatile anaesthetics are approximately doubled in children when compared with adults (Gregory, Eger and Munson, 1969) so that greater maintenance concentrations are required. The likelihood of e.e.g. changes and seizure-like activity is increased in children with enflurane (Goudsouzian and Ryan, 1976).

Ketamine is a further possibility in repeated anaesthesia. It is used extensively in paediatric anaesthesia for operative and diagnostic procedures. The major advantage of its use in children is that the frequency of psychic disturbance on emergence from anaesthesia is much less than in the adult (Sussman, 1974). Unfortunately, there have been a few reports of post-anaesthetic psychological reactions lasting several months in children following the use of ketamine (Meyers and Charles, 1978). Mehta, Dugmore and Raichand (1972) showed that ketamine was of little value in major extra- and intraocular surgery on account of undesirable eyelid, eyeball and gross head movements. On the other hand, it has been shown to have little or no effect on the intraocular tension (Ausinsch et al., 1976) and its use in anaesthesia for examination of the eye is valuable especially when repeated estimations of intraocular tension are required as in the management of glaucoma. Ketamine is also useful in the management of children undergoing radiotherapy, and this is discussed later. The original claim that lung ventilation was not depressed and that laryngeal reflexes were maintained has been shown to be only partially correct, in that respiratory depression, although short-lived may occur after its i.v. use. Laryngeal reflexes may be overactive in the initial phase of anaesthesia, but during prolonged anaesthesia they become obtunded and careful supervision of the patient by an anaesthetist is essential (Taylor, Towey and Rappaport, 1972). Its use is associated with increased salivation and this can lead to laryngeal spasm in the presence of increased laryngeal activity. The use of atropine before the administration of ketamine is advisable. For short procedures, i.v. ketamine 2 mg kg^{-1} can be administered with incremental doses of 1 mg kg^{-1} thereafter. Alternatively, the drug can be used i.m. in a dose of 10 mg kg^{-1}, although the onset of action may be delayed for about 5 min; a combination of i.v. ketamine, which produces anaesthesia within 1–2 min, and i.m. injection provides satisfactory anaesthesia for a period of about 20 min.

The psychological trauma of repeated anaesthesia and surgery can be reduced by the use of day-care facilities. An outpatient regime is particularly suitable for a large number of minor ophthalmic procedures (table I) in that they are of short duration, are performed in otherwise healthy children and are usually painless; the patient does not need to be restrained afterwards and analgesics are usually not required after operation. Young patients and their parents benefit from such arrangements and the economic advantage in terms of bed occupancy are well known; in addition, the frequency of hospital-acquired infection can be reduced by half (Otherson and Clatworthy, 1968). As in all day-case surgical units, the surgeon and anaesthetist must determine in advance the contraindications to outpatient surgery and, therefore, the patient should be examined carefully by the anaesthetist before the procedure. Some of the chronic disorders do not necessitate admission to hospital—asthma, controlled epilepsy, cerebral palsy and uncomplicated congenital heart disease; however, renal and hepatic disease, diabetes and coagulation disorders should constitute an indication for hospital admission. The methods of anaesthesia should be simple and recovery should be rapid. Halothane remains the agent of choice, although enflurane may be used in older children in whom the frequency of excitatory phenomena is less. Tracheal intubation is not contraindicated in outpatients; tubocurarine 0.05 mg kg^{-1} may be administered before the use of suxamethonium to prevent the development of muscle pains after operation (Bush and Roth, 1961). We use ketamine in outpatients for the measurement of intraocular pressure, but the prior administration of atropine is essential and recovery from anaesthesia may be prolonged. Patients should be fully awake before being allowed to return home; some centres observe patients for 4 h after the removal of an endotracheal tube, but this should not be necessary in normal circumstances. About 1% of patients develop complications requiring admission to hospital (Ahlgren, Bennett and Stephen, 1971), the commonest being repeated vomiting, persistent drowsiness and minor respiratory stridor.

Monitoring

The use of transparent plastic drapes enables the anaesthetist to observe the child who might otherwise be totally shrouded; the plastic drape is efficient in retaining heat, an important factor, particularly in the very young. As 60% of heat loss in the small child is lost by radiation, a radiant heater as used in open incubators is the best source of heat and is particularly useful during ophthalmological procedures as it does not interfere with surgical access. An alternative is the hot air blanket (Lewis, Shaw and Etchells, 1973). The increased heat loss in small children, the increased risk of malignant hyperpyrexia associated with ophthalmic procedures and the occurrence of benign hyperpyrexia with draping (Fraser, 1978) necessitate temperature monitoring. In most routine cases, an axillary probe will be adequate. The routine use of a precordial stethoscope is recommended in paediatric anaesthesia (Boulton, 1979), as is an e.c.g. monitor. Arterial pressure can be measured accurately and in a non-invasive manner using the Doppler ultrasonic technique; the accuracy compares favourably with invasive i.a. methods (McLaughlin et al., 1971) and is particularly appropriate if induced hypotension is used.

ANAESTHESIA FOR SPECIFIC PROCEDURES

Strabismus correction. Strabismus correction is by far the most commonly performed procedure in a paediatric ophthalmic unit (table I). Problems associated with this operation include the occurrence of the oculocardiac reflex, and the association with malignant hyperpyrexia. Preoperative sedation should be administered orally and thereafter anaesthesia may be induced i.v. or by an inhalation technique. The appropriate dose of atropine should be administered i.v. at this time. Access to a vein should be maintained as further atropine may be required. In very young children, ventilation of the lungs should be controlled; tubocurarine is a suitable neuromuscular blocking drug. Anaesthesia comprising nitrous oxide in oxygen may be supplemented with a narcotic drug or a volatile agent. In older children, nitrous oxide in oxygen with halothane or enflurane and spontaneous ventilation is very satisfactory. After surgery, the tracheal tube should be removed while anaesthesia is still of a sufficient depth to prevent coughing and laryngeal spasm. The patient should be supervised and allowed to awaken in the lateral position.

Intraocular surgery. The major problem concerns the control of intraocular pressure (Holloway, 1980). It is virtually impossible to prevent coughing and crying in young children, but the use of drugs administered orally before operation obviates the need for painful injections. An antiemetic drug will reduce the frequency of vomiting after operation. The techniques of induction are as described for strabismus correction; the importance of i.v. atropine is emphasized. Tubocurarine is the neuromuscular blocking drug of choice; its rapid onset of action in children renders it eminently suitable for facilitating tracheal intubation. The same procedure may be adopted for the management of patients requiring corneal grafting and cryosurgery or photo-coagulation for retinal detachment.

Dacryocystorhinostomy, tear duct operations and eyelid surgery. The principles outlined above should provide good operating conditions; however, occasionally techniques of induced hypotension may be of value.

Minor surgery and examination under anaesthesia. The use of the Rendell-Baker–Soucek mask (Rendell-Baker and Soucek, 1960) permits good access to the eye without the necessity for tracheal intubation and is very suitable for brief procedures and for outpatients. The advantages of ketamine anaesthesia for measurement of intraocular pressure have already been mentioned.

Radiotherapy. Radiotherapy is used in the treatment of tumours such as retinoblastoma and rhabdomyosarcoma, and the former may occur in the very young infant. Treatment consists of external radiation using, for example, the linear accelerator, and after an initial examination which includes measurements for the construction of a mould, the child receives a series of exposures (usually three sessions weekly for a period of 4 weeks). General anaesthesia is almost always required for the initial examination and need not differ from that required for other minor ophthalmological procedures. The subsequent treatment sessions are of very short duration and only babies and very young children need to be sedated. Various drugs have been used to provide basal narcosis, but currently a technique using ketamine i.m. offers many advantages (Sandford and Jones, 1976; Edge and Morgan, 1977). The actual duration of therapy is probably only 2 min, but an additional 5–10 min is required to ensure accurate positioning. During the period of exposure to radiation, the child is unattended and the anaesthetist must ensure that efficient monitoring of lung ventilation is available. We use closed-circuit television of the patient and an infrared carbon dioxide analyser to monitor the expired carbon dioxide concentration from a catheter positioned in close proximity to the child's face. Obviously, equipment for resuscitation must be immediately available. This technique has proved to be very satisfactory and obviates the problems of repeated anaesthesia of the more conventional type. Tolerance to ketamine has been reported by Bennet and Bullimore (1973) in children undergoing repeated radiography, but was not observed in the series of Edge and Morgan (1977).

Injuries to the eye. Trauma is not the most prevalent cause of blindness in the world, but is the commonest cause of unilateral loss of vision (Editorial, 1976), and it is an unfortunate fact that the frequency of ophthalmic trauma in children is relatively high and that damage is often serious (Duke-Elder, 1972). Almost all children will require anaesthesia for even the most minor examination of ophthalmic injury. Typically, the child is frightened and crying and may have ingested food or fluid shortly before the injury was sustained. As in all cases of trauma, priority should be given to the exclusion of other injuries; any associated head injury or trauma to the thorax or abdomen should receive prompt and efficient treatment. In the majority of instances, ophthalmic surgical intervention is not required immediately and some time may be spent in resting the patient, and in providing analgesia and sedation if required. It may be possible to delay the induction of anaesthesia until a satisfactory interval has elapsed since the ingestion of food, but it must be emphasized that, following trauma, the risks of regurgitation and vomiting persist after the conventional period of fasting has been observed. In the awake child, any attempt to introduce a nasogastric tube would cause a potentially disastrous increase in intraocular tension. A penetrating injury of the eye is often associated with prolapse of intraocular contents. It is essential that the induction of anaesthesia is not complicated by coughing and straining, and that the trachea is intubated rapidly and atraumatically. Unlike the injured adult, the injured child will probably have precipitated more damage in the perforated eye by crying and by rubbing the eye before and during admission to hospital than will be seen in association with any increase in intraocular pressure caused by suxamethonium. The advantages of rapid, atraumatic intubation will almost certainly outweigh any disadvantage of the use of suxamethonium. In the child, tubocurarine given i.v. with an induction agent can provide good conditions for intubation almost as rapidly as does suxamethonium and this technique offers an alternative in the presence of a full stomach.

MANAGEMENT AFTER OPERATION

Severe pain is uncommon after ophthalmic surgery, but conjunctival irritation occurs frequently and may be distressing. Morphine 0.2 mg kg^{-1} or papaveretum 0.3 mg kg^{-1} i.m. provide analgesia and prevent restlessness, and the effects of an antiemetic drug before operation will persist during the period after operation; in the absence of pain, diazepam 0.2–0.4 mg kg^{-1} is recommended for sedation. Blood loss is not a feature of eye surgery but, after prolonged procedures, young children will require i.v. fluids until the oral route of intake is re-established. All fluids should contain at least 5% dextrose, and a simple maintenance regime is:

Weight (kg)	Fluid (ml kg^{-1} h^{-1})
Newborn	3.0
4–10	4.0
10–20	3.0
20+	2.5

ACKNOWLEDGEMENTS

We are grateful to Dr J. Dudgeon and to Dr A. R. Russell for their advice in the preparation of this manuscript.

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LOCAL ANAESTHESIA AND THE EYE

E. D. ALLEN AND A. R. ELKINGTON

Eye surgery

The techniques of local anaesthesia are of crucial importance to the eye surgeon for, if need be, he can perform most of the operations in his repertoire with these methods; but the co-operation of an anaesthetist who fully understands the implications of these techniques (as well as having the usual skills of his specialty) contributes greatly to the care of patients with eye problems. Such co-operation means that the choice of anaesthesia can range from topical local block and neuroleptic agents to general anaesthesia. Proper team work should result in the ideal anaesthetic being chosen.

Local anaesthesia is popular with surgeons practising in those countries where eye disease is rampant and facilities for general anaesthesia are totally inadequate. The methods of achieving such anaesthesia may be learned quickly by relatively inexperienced auxiliaries, leaving the surgeon free to concentrate on the essentials of the operation. The hundreds of thousands who have had their sight restored in the eye camps held in the Indian subcontinent bear witness to the advantages of this approach.

There are staunch advocates of local anaesthesia even in those countries in which the anaesthetic services are well developed. These protagonists argue that many patients admitted to hospital for eye surgery are elderly and that general anaesthesia is often contraindicated, because of either cardiovascular or respiratory disease. They claim too, with justification, that they can operate on more patients in a given time than is possible under general anaesthesia and this is an important consideration when theatre time is short.

Local anaesthesia has its limitations, of course. It is usually inappropriate when children undergo surgery and there are many adults who cannot face the prospect of an operation being performed on their eye whilst they are conscious. General anaesthesia has the great advantage of ensuring a completely immobile eye, so necessary when surgery is carried out under the microscope—an increasingly common practice. In addition, the intraocular pressure may be reduced by a general anaesthetic, which helps lessen the risk of vitreous loss and other complications arising during intraocular surgery. And all but the most extrovert surgeons find teaching trainees much easier when the patient is asleep.

The following account, which is set out on a largely topographical basis, describes some of the commoner methods used to achieve anaesthesia, and indeed akinesia, by local techniques.

SEDATION

Patients awaiting an eye operation are likely to be anxious and adequate sedation is of prime importance. Such medication should properly be prescribed by an anaesthetist, who is best trained to appreciate the effects of the drugs used on the patient's vital functions. He is most likely to understand any interaction of the sedative with drugs either taken by the patient before operation or used during the operation. These may include not only the local anaesthetic itself but adjuvants, such as adrenaline, or solutions given either as drops or by intraocular injection, usually aimed at controlling the size of the pupil.

METHODS OF ANAESTHESIA

Lids

The removal of superficial skin lesions, such as papillomata or retention cysts, requires no more than local infiltration of an anaesthetic agent. Lignocaine (1% or 2% solution), with or without adrenaline 1 in 100 000 to minimize bleeding, is widely used. The use of adrenaline has its dangers in those who are hypertensive or taking monoamine oxidase inhibitors. The plunger of the syringe should be withdrawn at intervals during the course of the injection to detect if a blood vessel has been entered inadvertently. The addition of hyaluronidase promotes the dissemination of the local anaesthetic in the tissues and hastens the onset of the anaesthetic effect.

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0007-0912/80/070689-06 $01.00

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Many procedures, such as those to correct malposition of the lids (e.g. ectropion or entropion) or the excision of an infiltrating lesion (e.g. basal cell carcinoma) require that the whole thickness of the lid be anaesthetized. This also applies when the lids are fused (tarsorrhaphy), which is necessary to achieve protection of the exposed cornea.

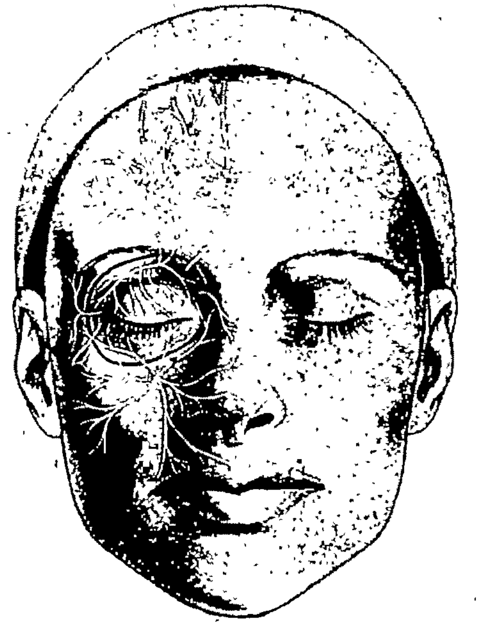

FIG. 1. Branches of the trigeminal nerve supplying the lids.

Figure 1 shows the points of exit of the branches of the trigeminal nerve which supply the lids and figure 2 illustrates the neurovascular plane in which they lie. If the lid alone is to be anaesthetized, this is most readily achieved by infiltrating a small amount of anaesthetic solution into the plane in which the nerves run—between the orbicularis oculi muscle and the tarsal plate. The area should then be gently massaged. When more extensive surgery, such as flap rotation or "Z-plasty", is envisaged, then it is preferable to block a specific nerve.

Most operations carried out on the lower lids and the cheek can be performed after blocking the infraorbital nerve at its exit from the infraorbital foramen. This lies 5 mm below the infraorbital margin, directly below the supraorbital notch (fig. 3). The extreme lateral part of the lower lid is supplied by the lachrymal nerve and local infiltration of this area is advisable. The extreme medial parts of the upper and lower lids are supplied by the infratrochlear nerve, and this can be blocked by infiltration at a point 3–4 mm below the junction of the upper and medial walls of the orbit (fig. 4). The remainder of the upper lid is supplied by the supraorbital and the supratrochlear nerves and these may be blocked at their appropriate exit points.

Surface of the globe

Anaesthesia of the cornea and bulbar conjunctiva may be necessary to allow proper examination of the damaged eye. Topical anaesthesia is also used before the removal of corneal foreign bodies and for minor surgery to the cornea or conjunctiva.

Several mild, short-acting anaesthetic agents are available which may be used for either brief examination or removal of superficial foreign bodies, for example proxymetacaine hydrochloride 0.5% (Ophthane) and oxybuprocaine (Benoxinate). However, for more extensive procedures, two agents have become established as being particularly useful; cocaine 4% and amethocaine 1%.

Cocaine produces vasoconstriction and is preferred for conjunctival operations. It has a mydriatic effect and is therefore contraindicated in patients predisposed to angle-closure glaucoma. The other major disadvantage is the drug's effect on the corneal

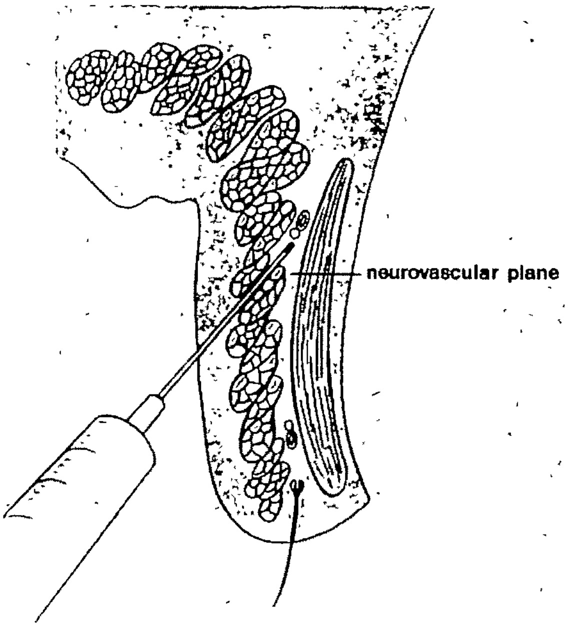

FIG. 2. The neurovascular plane lies between the orbicularis oculi muscle and the tarsal plate.

epithelium, which may become cloudy or even desquamate a few minutes after the instillation of the drops. The use of cocaine is therefore contra-indicated in any surgery where a good view through the cornea is essential, as in retinal detachment surgery. Amethocaine, if used frequently, has a similar but lesser effect on the corneal epithelium. The disadvantage of amethocaine is that it may cause vascular dilatation and hence precipitate bleeding.

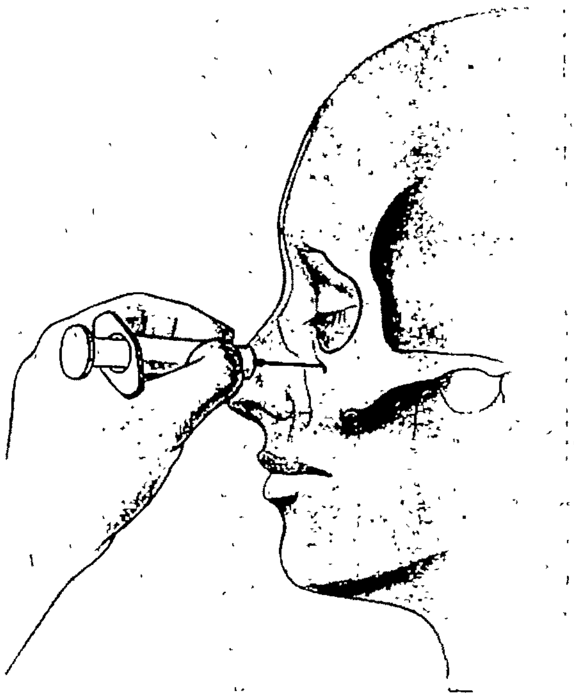

FIG. 3. Blocking the infraorbital nerve.

Once the cornea has been anaesthetized, the afferent limb of the protective blink reflex is lost, and the eye becomes vulnerable to accidental damage. It is therefore important to protect it from trauma by means of a pad firmly applied over the closed lid. The pad should be left in place for several hours, by which time corneal sensation will have been fully restored. If the pad is only loosely applied the lid may open beneath it and the cornea be abraded by the pad itself. It is the risk of such accidental damage and the toxicity to the corneal epithelium that preclude the repeated use of local anaesthetic drops in those painful but transient conditions such as corneal abrasions or when the cornea is damaged by ultraviolet light.

Intraocular operations

The achievement of anaesthesia for intraocular surgery is exacting, for several requirements must be satisfied.

Sedation. The patient must be sedated so that he lies still during the operation and does not cough or strain. Sudden movements when instruments are within the eye can be disastrous. Straining and coughing lead to engorgement of the veins in the orbit and hence an increase in intraocular pressure because the venous sinuses in the choroid become distended. This may result in prolapse of the iris and, more seriously, the vitreous when the eye is incised. If vitreous becomes trapped in the wound a fibrous reaction may develop which leads to distortion of the pupil and traction on the retina which may precipitate a detachment.

Sedation is usually achieved by the use of benzodiazepine drugs or opiates and these are frequently combined with an antiemetic to reduce the likelihood of vomiting in the period after operation.

Anaesthesia of the cornea and bulbar conjunctiva is achieved topically as described earlier.

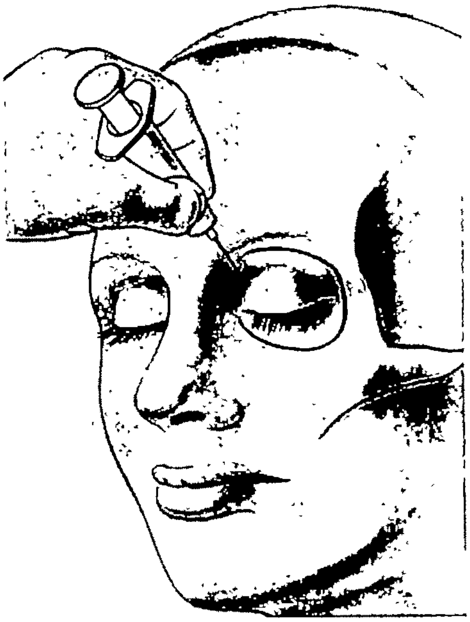

FIG. 4. Blocking the infratrochlear nerve.

Intraocular anaesthesia. The iris is the most sensitive structure within the eye and it must be anaesthetized before any intraocular surgery is undertaken. This is achieved by giving a retrobulbar injection. The pain fibres arising in the iris leave the globe posteriorly, in either the short ciliary nerves which run backwards to the ciliary ganglion (fig. 5) or the long ciliary nerves. The fibres entering the ganglion pass straight through it to form the sensory root which joins the naso-ciliary nerve. The long ciliary nerves, which pass close to the ganglion, also join the naso-ciliary nerve. Hence, the iris is conveniently anaesthetized by the infiltration of an anaesthetic solution around the ciliary ganglion.

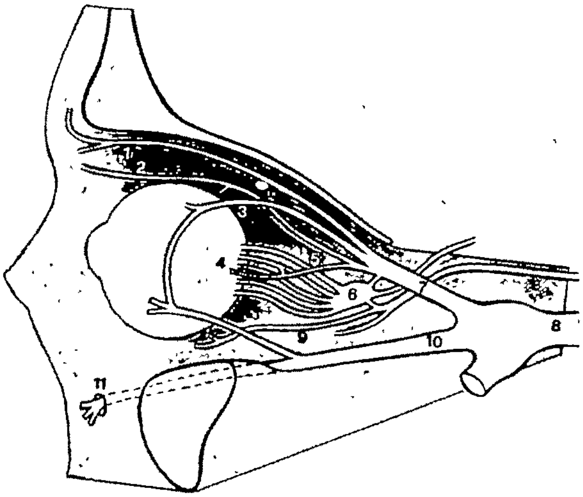

FIG. 5. The ciliary ganglion (6) and the associated nerves. 1 = frontal nerve; 2 = infratrochlear nerve; 3 = lachrymal nerve; 4 = short ciliary nerves; 5 = long ciliary nerves; 6 = ciliary ganglion; 7 = ophthalmic nerve; 8 = sensory root of trigeminal nerve; 9 = nerve to inferior oblique; 10 = maxillary nerve; 11 = infraorbital nerve.

The ganglion lies about 1 cm from the optic foramen, between the optic nerve and the lateral rectus muscle, within the muscle cone. It is reached by giving a retrobulbar injection, using a 4-cm long 25-gauge needle.

The patient is asked to look upwards and medially, thus drawing forward the fascial sheath running between the inferior and lateral rectus muscles. The needle is inserted through the skin at a point just above and medial to the junction of the floor and the lateral wall of the orbit (fig. 6). Alternatively, the lower lid may be drawn down and the injection given directly through the conjunctiva. The needle should be passed straight backwards for about 1 cm. The eye moves slightly as the needle pierces Tenon's capsule (the fascia encompassing the globe and its associated muscles). The needle is then directed upwards and medially, towards the apex of the orbit, and inserted a further 2 cm. Its tip should then lie within the muscle cone, adjacent to the ciliary ganglion. Lignocaine 1 or 2 ml (or 2–3 ml if hyaluronidase has been added) is injected slowly.

The main complication of a retrobulbar injection is haemorrhage from one of the many small orbital veins being punctured. This causes immediate marked proptosis and the resulting venous engorgement increases the intraocular pressure. The operation must be postponed. Some surgeons try to lessen the risk of precipitating haemorrhage by slowly injecting a small amount of the anaesthetic as the needle is advanced, in the hope that any small blood vessels will be pushed away from the needle tip.

A beneficial side-effect of a retrobulbar injection is a slight decrease of the intraocular pressure, probably because of constriction of the posterior ciliary arteries.

Akinesia. Paralysis of both the facial and the extraocular muscles is necessary for safe intraocular surgery. Contraction of the orbicularis oculi causes the lids to press upon the eye and contraction of the extraocular muscles leads to distortion of the globe. Both these events cause an increase in intraocular pressure, should the eye be intact; if an incision has

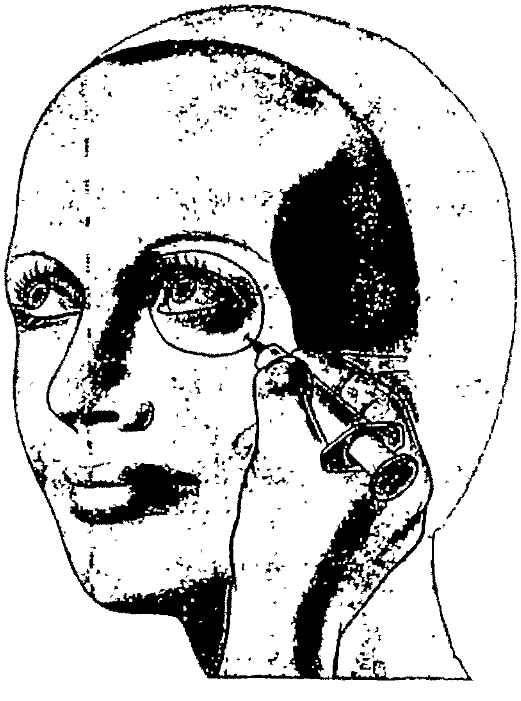

FIG. 6. Retrobulbar injection.

been made through the globe's outer coat its contents, including vitreous, may be expelled.

Akinesia of the orbicularis oculi can be achieved by the methods of O'Brien or Van Lint.

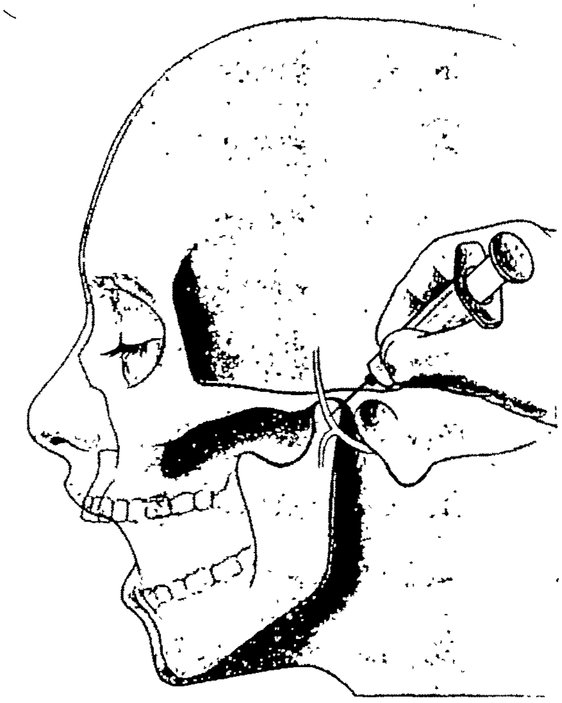

FIG. 7. Blocking the facial nerve (O'Brien's method).

The course of the facial nerve is shown in figure 7. In O'Brien's method the condyle of the mandible is first identified with the finger by asking the patient to open and close his mouth. The needle is inserted through the skin at a point overlying the junction of the upper and middle thirds of the ramus of the mandible. The needle is passed directly down to periosteum, and withdrawn slightly, before the injection of 2–3 ml of anaesthetic solution. The area is then massaged. The effect of the injection is to block the tempero–facial branches of the facial nerve. This method has the potential disadvantage that any communicating branches from the mandibulo–facial trunk of the nerve, which join the tempero–facial trunk distal to the site of this injection, are inevitably missed.

Van Lint's method involves injecting anaesthetic solution across the zygomatic bone as it forms the lateral and inferior margins of the orbit (fig. 8). The needle is inserted 1 cm lateral to and below the outer canthus and the injection is made beneath the muscle fibres upwards towards the eyebrow. The needle is almost fully withdrawn and passed downwards and medially towards the infraorbital foramen and the tissues infiltrated. A total of 4 ml of anaesthetic solution is given. This method has the advantage of being more peripheral and therefore the consequence is that any distal communicating branches will be blocked. A possible disadvantage is bleeding into the lids. The resulting haematoma may cause pressure on the eye, with all the attendant problems.

Akinesia of the extraocular muscles is a fortunate consequence of the retrobulbar injection, because the motor nerves lie on the inner surfaces of the recti and are blocked by the anaesthetic within the muscle cone.

Lachrymal system

Surgery on the lachrymal drainage system is commonly undertaken either to restore patency or to eradicate infection. When the adult naso–lachrymal duct is obstructed, part of the medial wall of the orbit may be removed and the mucosa of the lachrymal sac anastomosed to that of the nasal cavity (dacryocystorhinostomy—DCR). Persistent sepsis of the system,

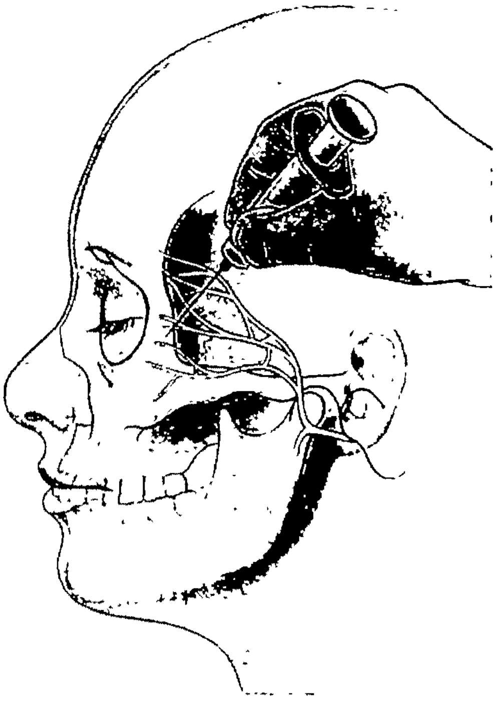

FIG. 8. Blocking the facial nerve (Van Lint's method).

particularly in the elderly or infirm, may justify excision of the sac (dacryocystectomy).

Such surgery requires anaesthesia of the skin of the inner canthus, the medial part of the lower lid and the lachrymal canaliculi and contents of the lachrymal fossa. For DCR the nasal mucosa should be anaesthetized.

Skin anaesthesia is achieved by blocking the infratrochlear and the infraorbital nerves as described earlier. The lachyrmal fossa and the mucosa of the lateral wall of the nose are innervated by branches of the anterior ethmoidal nerve which can be blocked by an injection placed about 2 cm behind the orbital margin at the junction of the roof and medial wall. Further anaesthesia of the nasal mucosa may be provided by packing the nose with ribbon gauze soaked in a mixture of cocaine and adrenaline. Haemostasis is best achieved by packing 30 min before the operation.

Pain

Occasionally a patient presents with an extremely painful blind eye. This problem is less common than formerly thanks, in part, to the control of ocular inflammation with steroids and the introduction of drugs which control glaucoma. However, there are still patients whose ocular pathology cannot be controlled and whose eye becomes both blind and painful. In such cases a retrobulbar injection of alcohol, aimed at destroying the sensory nerves, may secure total relief from the pain and allow retention of the eye, which may still be cosmetically acceptable.

The technique of giving the injection has been described earlier, but it should be realized that the introduction of a concentrated solution of alcohol into the orbit is excruciatingly painful. It is therefore essential first to inject a small amount of anaesthetic, preferably a long-acting solution, such as bupivacaine. After the injection of the anaesthetic the needle can be left in position and after 2 or 3 min the syringe is changed and 1–2 ml of 80% or 90% alcohol is introduced. Should the pain not be completely eradicated the injection can be repeated a few weeks later.

Incidental corneal anaesthesia

The anaesthetic cornea is at risk irrespective of whether the anaesthesia has been induced intentionally or encountered incidentally. The corneae of all patients under general anaesthesia must be protected, as must those of other unconscious patients, some of whom will be under the care of the anaesthetist in an Intensive Care Unit. It is essential that the cornea be kept moist and, in the absence of blinking, which normally spreads a tear film with bacteriocidal properties over the surface of the cornea, prompt supportive measures are necessary. Drops of saline, liquid paraffin or artificial tears (Hypromellose) should be instilled frequently and antibiotic ointment (e.g. chloramphenicol) should be applied to lessen the risk of secondary infection.

A facial paralysis, such as that brought on by Bell's palsy, may lead to the eye becoming exposed as a result of inadequate closure of the lids. The cornea is at particular risk if inadequate closure is associated with corneal anaesthesia, as may occur following excision of an acoustic neuroma when the integrity of both the facial and trigeminal nerves may be jeopardized. The exposed cornea can become infected, leading to permanent scarring, or even perforation, in a matter of hours. In such cases, when recovery of the palsy is judged likely to be either delayed or incomplete, a tarsorrhaphy should be performed in good time. The operation should be carried out meticulously, for without due attention to detail, lashes may be left lying against the cornea which remain undetected behind the fused lids. The price the patient has paid for a hastily performed operation only comes to light when the tarsorrhaphy is opened to reveal an opaque cornea beneath the parted lids.

Many operations upon the eye can be performed under local anaesthesia and it is usually individual circumstances that dictate whether this technique is used of choice. Although eye surgeons are trained to achieve anaesthesia by local means, the co-operation of an experienced anaesthetist contributes greatly to the range of methods available for ensuring that the operation is performed under ideal circumstances. Sight is precious and the anaesthetist can play a crucial role in both its restoration and preservation.

ACKNOWLEDGEMENTS

It is a pleasure to thank Mr J. D. C. Anderson, F.R.C.S., now of the Noor Eye Institute, Kabul, Afghanistan, for help with the script and Mr P. G. Jack of the University Department of Teaching Media, who drew the diagrams.

Br. J. Anaesth. (1980), 52, 695

THE EYE AS A MIRROR OF SYSTEMIC DISEASE

F. CLIFFORD ROSE AND J. FASLER

Irrespective of speciality, examination of the eyes should be part of the routine physical examination. Quite apart from purely ocular disease, this will yield valuable information regarding systemic diseases, not least because the eye is the only part of the body where vascular and neurological tissue can be viewed directly.

EXAMINATION

Whilst full ophthalmological examination is time-consuming, a rapid examination can pick up many significant abnormalities. The bulbar and tarsal conjunctival surfaces should be inspected for signs of inflammation, haemorrhage, anaemia and jaundice.

Using a small hat-pin, visual fields can be assessed surprisingly accurately by confrontation, a relative field loss being detected if the head of a red pin loses colour at any point. Using this technique, even an enlarged blind spot can be found, but field defects will need to be confirmed with formal perimetry.

Examination of the pupils will reveal asymmetry or irregularity; generally speaking, the older the patient the smaller are the pupils. Light reflexes, both direct and consensual, should be tested as well as pupil constriction with convergence.

It is usually possible to examine the optic discs through an undilated pupil, but if a full fundus examination is necessary the pupils may be dilated with a short-acting mydriatic such as cyclopentolate. This is contraindicated in patients with glaucoma and those whose consciousness is fluctuating or who need neurological observation following a head injury or surgery. The optic discs are examined first and then the retinal arteries and veins are followed out to the four quadrants of the retina. Particular attention should be paid to the area of the macula 1½ disc diameters on the temporal side of the optic disc, since even minor abnormalities in this region produce a profound decrease in visual acuity.

The face should be studied to exclude asymmetry of the eyes; for example one eyeball may be depressed if there is a tumour involving the orbit or a vascular anomaly in the cavernous sinus. Ptosis or inability to close the eyelids may be the result of a weakness of the orbicularis oculi muscles, resulting from a VIIth (facial) nerve palsy. Lid retraction with white sclera visible between the iris and eyelids is evidence of thyroid disorder.

The best test of function is to measure the visual acuity, using a reading test type for near vision, and a Snellen chart for distance vision, via a pin-hole to eliminate refractive errors if necessary. If these charts are not available, reasonable assessments can be made with various sizes of newspaper print. If the vision in one eye is greatly reduced compared with the other, enquiry may reveal that the affected eye has been "lazy" (amblyopic) since childhood.

External ocular movements should be tested next, but even if normal it is important to ask the patient whether he sees double as diplopia can occur without clinical evidence of impairment of ocular movements. The presence of nystagmus should also be noted with regard to the direction of the slow and fast phases.

Neurological abnormalities

Cranial nerve lesions

A IIIrd nerve palsy is not uncommon and can be recognized easily by ptosis; with the lid raised the affected eye will be fixed in abduction with a dilated unreactive pupil. A pupil-sparing IIIrd nerve palsy indicates vascular disease (hypertension or diabetes) rather than compression (aneurysm or tumour). A subdural haematoma is more likely to affect the VIth cranial nerve (producing paralysis of abduction), even though it does not have as long an intracranial course as the IVth. It is the nerve most frequently affected by increased intracranial pressure, meningitis or intracerebral haemorrhage. The commonest single cause of an isolated IVth cranial nerve palsy is a head injury, which need not necessarily be severe. In the unconscious patient, a fixed dilated pupil is one of the earliest signs of tentorial herniation.

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Frequently abnormalities of more than one oculomotor nerve are found. A compressive lesion within the cavernous sinus, such as a pituitary tumour, metastatic carcinoma or aneurysm of the internal carotid artery, may affect all three cranial nerves as well as resulting in other symptoms, such as proptosis, pain behind the eye and, in the case of a carotid cavernous fistula, a loud buzzing noise audible on auscultation as a bruit. The finding of a IIIrd, IVth or VIth nerve palsy provokes a search for a surgically remediable cause but, in many cases, especially in the older age group, the cause is an occlusive lesion of the blood vessels serving these nerves and indicative of generalized disease. The commonest is diabetes mellitus, which usually affects the IIIrd nerve but does not often involve the pupil. Pain may occur in diabetic ocular palsies, as with an aneurysm, but it is usually short lived.

The other main cause of arteriopathic ocular palsy is hypertension and sometimes a hyperlipidaemia is also found. Treatment consists of controlling the arterial pressure and any lipid abnormality. Before the age of 40 yr, multiple sclerosis should be considered as a possible cause of ocular palsy. Another cause of isolated cranial nerve palsy in younger patients is sarcoidosis, the facial nerve being the commonest affected. Other systemic disorders affecting isolated ocular motor nerves are less common, for example connective tissue disorders, such as polyarteritis nodosa or systemic lupus erythematosis, ascending polyneuritis (Guillain–Barré syndrome) and meningo–vascular syphilis; examination for treponemal serology in the blood and c.s.f. should not be forgotten.

Diseases of the ocular muscles and neuromuscular transmission

The commonest cause of an impairment of ocular movement involving the external ocular muscles directly is thyroid eye disease. Frequently, only elevation of the eye is affected but there are often other signs, such as proptosis, lid retraction and lid lag.

A space-occupying lesion within the orbit will affect ocular movement and result in proptosis and pain, in which case CT scanning of the orbits is a fruitful investigation. It may be necessary to biopsy a discrete mass, either directly or via the ethmoidal route, since orbital secondaries from various sites such as bronchus, breast or kidney are well recognized.

Sometimes, a mass may appear to be a diffuse increase in intra-orbital soft tissue or may arise from the external ocular muscles themselves; this condition is known as orbital pseudo-tumour and the diagnosis is confirmed by biopsy, which will usually reveal granuloma formation. Orbital pseudo-tumours are frequently painful and respond to treatment with steroids and azathioprine; if left untreated, visual loss as a result of compression of the optic nerves may result.

Proptosis can also occur if the orbit is invaded from the frontal sinus by tumour or mucocoele and suggestive symptoms include nasal or blood-stained post-nasal discharge, or frank epistaxis. Wegener's granuloma affecting the naso–pharynx or sinuses may also invade the orbit directly.

A genetically determined disorder affecting the external ocular muscles is progressive external ophthalmoplegia; this is an ocular muscular dystrophy presenting usually in the second or third decades with bilateral ptosis followed by symmetrical loss of ocular movements. In a few cases other muscle groups may be affected; the diagnosis is confirmed by electromyography and muscle biopsy.

Myasthenia gravis. The external ocular, orbicularis oculi and levator palpebrae muscles are amongst the most frequently affected in myasthenia. Some cases remain confined to these muscles when the disease generally has a benign course. The characteristic feature in the history is the fluctuation in symptoms such as diplopia or ptosis during the day so that they are worse in the evening or after exercise. On examination fatiguability of the affected muscles is elicited. The most widely used diagnostic test is the edrophonium (Tensilon) test. It is sometimes difficult to assess the result in mild cases when a therapeutic trial of anticolinesterases such as neostigmine or pyridostigmine may be justified. In cases with a more peripheral distribution, single fibre electromyography can assist in diagnosis. Ninety per cent of patients with myasthenia have increased antibody to acetyl choline muscle receptors, but this test is not yet widely available. Ocular myasthenia can usually be treated with anticolinesterase drugs alone, although the results are not always satisfactory, and other measures such as ptosis splints or muscle resection may be needed. (Widespread myasthenia may be treated with steroids, thymectomy or plasmaphoresis. Symptoms of dyspnoea and dysphagia must be taken seriously and assisted ventilation considered if lung function is markedly reduced.)

The pupil

The value of pupillary reactions in assessing neurological states following head injury (particularly in connection with a subdural or intra-cerebral haemorrhage) is well known, as are the contraindications to instilling mydriatic drops in such cases. The well-known Argyll Robertson pupil is classically small and irregular, not responding to light, but responding to accommodation. Although usually associated with neuro-syphilis, it can occur with diabetes mellitus and multiple sclerosis.

Adie's myotonic pupil is usually unilateral and found in young women, where the patient frequently notices dilatation of one pupil and may complain of blurring of near vision. On casual testing the affected pupil may not appear to react to light at all, but will dilate slowly in response to prolonged darkness and contract again slowly when re-exposed to light; response to accommodation and convergence is also slow. A brisk response to dilute pilocarpine is a useful diagnostic test. In some patients tendon reflexes are absent, although there are not usually other nervous system signs. Treatment other than reassurance is rarely required.

A unilateral constricted pupil with partial ptosis, endophthalmos and anidrosis of the ipsilateral side of the face are characteristic of Horner's syndrome, although the latter two signs are notoriously difficult to detect. This results from a lesion of the sympathetic nerve supply anywhere from the brain stem to the ciliary ganglion which provides stimulatory fibres to part of levator palpabrae superioris and dilator fibres to the pupil; whilst occasionally congenital, the most important possibility to exclude is an apical carcinoma of the bronchus. The commonest cause is cluster headaches—a form of migraine. Other causes of Horner's syndrome are vascular lesions of the pons and medulla, syringomyelia and syringobulbia, cervical spondylosis, disc prolapse and cervical lymph nodes enlarged by infection such as tuberculosis, or by lymphoma or secondary tumour. It occasionally occurs in multiple sclerosis and viral encephalitis.

A dilated unreactive pupil with ptosis and impaired ocular movements is characteristic of a IIIrd nerve palsy; in such cases the pupil has no consensual and no direct reflex, thus indicating that the lesion is in the parasympathetic fibres controlling the pupillary sphincter muscle, rather than in the optic nerve.

Another important sign is the relative afferent pupillary defect. In this sign there is little direct or consensual response to a light shone into the affected eye, but a brisk direct and consensual response when the light is shone into the unaffected eye. When the light is moved to the affected eye again, both pupils dilate. This phenomenon is best elicited by swinging the beam of a bright torch from one eye to the other fairly rapidly. Where there is marked optic atrophy and visual loss in the affected eye this sign does not provide any extra information but, in cases where the sign is positive, if the affected eye has good vision and the optic disc appears normal, it usually indicates a previous episode of optic or retrobulbar neuritis. This finding may assist greatly in the interpretation of neurological symptoms and signs found (Perkin and Rose, 1979).

Many systemic drugs may affect the pupillary responses, particularly if used in excess. Pin-point pupils may result from opiate administration, therapeutically or illegally, and dilated pupils can result from a large range of drugs with anticholinergic effects such as tricyclic antidepressants. This effect must be borne in mind when administering such drugs to patients with closed angle glaucoma in whom an acute attack may be precipitated.

The optic disc

The two basic abnormalities which may be seen in the optic disc in systemic disease are disc swelling and disc pallor.

A red swollen disc with blurred margins is frequently referred to as papilloedema, whatever the cause, but preferably this term should be restricted to swelling resulting from increased intracranial pressure produced by cerebral tumour, abscess, haemorrhage, hydrocephalus or other causes. In papilloedema, visual acuity is not affected and the only abnormality on visual field testing is enlargement of the blind spot. If the intracranial pressure is increased for a long period, the patient may notice brief episodes of loss of vision in the affected eye lasting a few seconds and associated with manoeuvres increasing intracranial pressure such as bending or straining. This is a result of intermittent obstruction of the arterial blood supply to the retina by pressure within the optic nerve and is usually termed an obscuration. It is a sign that, if the intracranial pressure is not decreased, permanent ischaemic damage to the disc and retina may ensue, since long-standing papilloedema can result eventually in optic atrophy.

The main causes of increased intracranial pressure are well known, but a syndrome now diagnosed more frequently is benign intracranial hypertension, where symptoms and signs of increased intracranial pressure are found without evidence of a space-occupying lesion or ventricular enlargement on cerebral CT scanning. A lumbar puncture (after a CT scan) will demonstrate increased c.s.f. pressure. The condition is most common in obese young women with menstrual irregularity, but there are numerous other causes, including steroid therapy, administration of tetracycline, naladixic acid, endocrine disorders and following head injury and middle ear disease. If left untreated, permanent visual loss may occur by the mechanism described above.

In disc swelling from causes other than increased intracranial pressure, the central vision and therefore visual acuity are affected early and visual field testing will demonstrate a central scotoma in the affected eye. In younger patients, by far the most common cause is optic neuritis, which characteristically presents as blurring of vision in the affected eye with pain on eye movement. This usually recovers after a few weeks, although the visual acuity may be slightly less than before the attack. The optic disc may become pale, but, if normal, the finding of a relative afferent pupillary defect will help elucidate what has occurred. In retrobulbar neuritis the same symptoms occur, but the disc appearance remains normal. If patients with optic neuritis are followed for a sufficient time, the majority will progress to develop lesions of multiple sclerosis (Perkin and Rose, 1979). Sometimes, neurological abnormalities are found at the time of an attack of optic neuritis even when the patient has not noticed other symptoms. Multiple sclerosis is still basically a clinical diagnosis, but supporting evidence may be obtained from visual evoked response testing (which shows a delay in the transmission of nerve impulses from the affected eye to the occipital cortex) and the finding of specific patterns of immunoglobulins (oligoclonal bands) in the c.s.f.

In patients of more than 50 yr, the most common cause of disc swelling is ischaemic papillopathy which results from small vessel vascular disease. This syndrome presents with painless loss of vision occurring over several hours. The field defect is a central scotoma extending irregularly outwards with areas of preserved vision; in some cases only the upper or lower halves of the visual field are lost, whilst in others a crescentic area of the visual field is lost with sparing of central vision.

Optic atrophy frequently follows periods of optic disc swelling, but may occur without disc swelling, when the optic nerve is directly compressed by a tumour, such as a sphenoid ridge meningioma. In such cases a cerebral CT scan is invaluable. Optic atrophy may also follow retinal disease, but this is usually obvious on ophthalmoscopy.

Visual field defects

Plotting visual fields can assist greatly in the siting of an intracerebral lesion. Direct pressure on an optic nerve gives a central scotoma, but lesions compressing the crossing fibres of the optic chiasm, for example pituitary tumours, craniopharyngiomas and internal carotid aneurysms, will give rise to classical bitemporal hemianopia. These lesions can be missed on CT scanning so that, if the field defect is definite, it is sometimes necessary to proceed to air encephalography or exploratory craniotomy on the basis of the visual field defect alone.

A lesion of the cerebral cortex posterior to the chiasma, involving the optic tract or radiation, will result in a homonymous hemianopia; if of slow onset, a cerebral tumour should be sought. If there is a history of sudden onset of loss of part of the visual field, this usually indicates a vascular cause; characteristically infarction of the occipital lobe produces an homonymous hemianopia with sparing of the central area as a result of the dual blood supply of the area of cortex relating to the macula and therefore central vision. Postoperative plotting of visual fields following removal of tumours, particularly those arising from the pituitary gland, can often give warning of recurrence even before there is any radiological evidence.

Hysterical blindness can usually be diagnosed on the basis of the patient's behaviour, normal ophthalmological appearances and bizarre field loss. A normal visual evoked response will provide instant confirmation of this diagnosis.

Inflammatory disorders

Uveitis

The iris, ciliary body and choroid comprise the uveal tract and involvement of one or all of these structures is a feature of a wide range of systemic diseases. Anterior uveitis involving the iris and ciliary body presents as blurred vision with a painful photophobic red eye, whereas posterior uveitis is usually painless. In more than half the cases of uveitis seen, no systemic association can be found—"endogenous" uveitis.

Probably the commonest systemic cause of uveitis in the world is onchocerciasis, but this is normally confined to developing countries. The most common infectious cause of uveitis in the United Kingdom is congenital toxoplasmosis, which can usually be diagnosed from its distinctive fundal appearance. Toxoplasma dye tests reflect intraocular activity poorly, so ophthalmological observation is the principal method of assessing progress. As this is basically an autoimmune process, steroids are necessary to reduce activity. Pyrimethamine and cotrimoxazole have not been shown to halt intraocular activity in these cases. Tuberculosis may be diagnosed on the basis of choroidal tubercle, and other rare infectious causes of uveitis include syphilis, brucellosis, leptospirosis and toxocara infiltration.

HLA typing has demonstrated a link between uveitis and certain systemic disorders. The HLA B27 group of diseases, including ankylosing spondylitis, Reiter's syndrome, ulcerative colitis and Crohn's diseases with arthropathy, may all give rise to uveitis. In such cases, however, the arthritic manifestations usually precede the ocular changes. HLA B5 has been found to be associated with Behcet's syndrome, the major features of which are iritis, thrombophlebitis and oro–genital ulceration. Many other systems such as the alimentary tract and the central nervous system are more rarely involved. The most serious ocular complication of Behcet's syndrome is the progressive obliteration of the retinal vasculature, which can result in complete blindness within a few years. It is important to make the diagnosis as the ocular changes respond poorly to treatment with steroids alone, whereas the addition of immunosuppressive drugs such as azathioprine and chlorambucil may at least retard the visual loss, if not prevent it completely.

In children, the commonest systemic cause of uveitis is Still's disease. Children at risk of developing uveitis can be identified by the fact that 80% of them will be positive for antinuclear factor, whereas only 30% of all patients with Still's disease are positive.

In young adults the commonest systemic cause of anterior and posterior uveitis is sarcoidosis and all such patients should be screened at least with a chest x-ray, Mantoux test (negative in the majority of cases of sarcoidosis) and serum calcium concentration. If any of these are abnormal or there are other suspicious features, more detailed investigations such as a Kveim test, alveolar transfer factor and bronchoscopy may be required. Sarcoidosis may also cause kerato–conjunctivitis sicca and conjunctival lesions. Frequently treatment with systemic steroids is necessary to control the ocular manifestations of sarcoidosis as well as involvement of other systems. Chronic uveitis resulting from sarcoid may have a poor prognosis, in spite of treatment.

Other connective tissue disorders

Other connective tissue diseases may affect the eye although they cause uveitis only rarely. Systemic lupus erythematosis may cause "cystoid bodies" in the retina and a positive DNA binding test is confirmatory.

There is no specific ocular appearance to polyarteritis nodosa, which causes scleritis; renal involvement may lead to the appearance of a hypertensive retinopathy. Rarely, it may cause anterior uveitis and retinal vasculitis, as may the related disease of Wegener's granuloma. Diagnosis of these two conditions usually depends on the histological appearance on biopsy of affected tissue such as kidney, lung or naso–pharynx. Polyarteritis nodosa may also be diagnosed from the characteristic appearances on mesenteric angiography.

By far the most common connective tissue disease is rheumatoid arthritis, the main ocular manifestation of which is kerato–conjunctivitis sicca syndrome, in which lachrymal and salivary gland output is diminished, resulting in dry, gritty eyes and difficulty in masticating and swallowing. It is one of the most difficult ocular conditions to treat satisfactorily. Rarely, rheumatoid involvement of the anterior sclera, usually a mild episcleritis, may progress remorselessly to perforation of the eyeball—"scleromalacia perforans".

Giant cell arteritis

This is one of the most important systemic diseases affecting the eyes in the elderly. A history of malaise, severe headaches, scalp tenderness, painful swellings in the temporal areas and pain on chewing are indications for measuring the erythrocyte sedimentation rate (e.s.r.). If this is increased, treatment with large doses of steroids, administered i.m., should be started and temporal artery biopsy carried out within 48 h to confirm the diagnosis. If left untreated, the catastrophe of central retinal artery occlusion and blindness in one or both eyes may ensue rapidly. Even if vision in one eye has already been lost, prompt treatment may save the other eye. It is worth remembering that this disease is not confined to the temporal and ophthalmic arteries; rarely, strokes resulting from the involvement of vertebral, carotid and intracranial arteries may occur and coronary artery occlusion has also been reported.

The syndrome of polymyalgia rheumatica has been shown to overlap with giant cell arteritis, and patients with this condition should be kept under long-term observation with checks of the e.s.r. at regular intervals. The pathogenesis of these two conditions is as yet unknown, but they are confined to patients of more than 50 yr. Rather surprisingly, it has been found that life expectancy is not reduced by giant cell arteritis, even though patients may require treatment with systemic steroids for years.

Viral infections of the eye

The eye is only rarely directly involved in systemic bacterial infections, but is far more commonly infected by viruses. Marked conjunctivitis may be a feature of adenovirus infections and conjunctivitis is frequently part of measles and influenza. More serious are herpes virus infections, especially in the elderly or immunosuppressed patients. *Herpes simplex*, while causing cold sores elsewhere, may result in a keratitic corneal ulcer. This usually responds to local idoxuridine, but disaster may occur if local steroids are administered without slit lamp examination. It is inadvisable to prescribe steroid drops for any eye condition before a specialist opinion has been obtained. *Herpes zoster* may involve the eye in shingles, if this involves the ophthalmic division of the trigeminal nerve. Here again, the mainstay of treatment is local idoxuridine. Many other viruses such as *Papovirus* and *Cytomegalovirus* may involve the eye, but these are not usually serious, except in the case of congenital cytomegalovirus disease.

Vascular disorders

Hypertension and vascular occlusion

Examination of the fundus is essential in the evaluation of the severity and duration of hypertension. The grading of hypertensive retinopathy is well known, but it is probably better to record the actual features of the retinopathy rather than the grade. Hypertension secondary to renal failure shows no specific features. The so-called "macular star" or hard exudates is a reflection of severe prolonged hypertension, rather than a direct result of renal impairment. Obviously, the more severe the retinopathy and thus the hypertension, the more likely the finding of renal failure as a cause, or result, of severe hypertension.

Visual loss is not usually a feature of uncomplicated hypertensive retinopathy, although the patients may notice blurred vision because of macular oedema when papilloedema is present. If there is sudden loss of vision in a patient with hypertension, this is usually produced by occlusion of either the arterial or the venous retinal circulation. These are more common in hypertensive patients, presumably because of more marked sclerotic changes in the vessels. In a central retinal artery occlusion, all retinal arteries are narrowed and attenuated and the retina is pale. In some cases only the short posterior ciliary vessels serving the optic discs are involved, in which case the appearance is that of a swollen disc with a relatively normal looking retina in the early stages. In both these cases the prospect for unimpaired vision is poor.

The appearance of a central retinal vein occlusion is more dramatic with widespread haemorrhages, dilated veins and retinal oedema. However, the prognosis is better, with gradual return of vision to near normal in some cases. In about 15% of cases, a secondary thrombotic glaucoma may ensue. There is no specific treatment for retinal arterial and vein occlusion although, if there is marked macular oedema, laser photocoagulation may be of benefit. Hypertension should of course be treated, but it is important not to reduce the arterial pressure too rapidly as reduced perfusion may result in cerebral or retinal ischaemia, the latter resulting in blindness.

Retinal artery and venous occlusion may also be found in association with hyperlipidaemia and in diseases where blood viscosity is increased, such as myeloma, polycythaemia and leukaemia and retinal vein occlusion is also found in association with diabetes.

Diabetes mellitus

The eye is frequently involved in diabetes. Diabetic neuropathy may involve cranial nerves, but blurring of vision is common when the diabetic state is not well controlled, because of dehydration of the lens. Cataracts occur in people with diabetes more frequently than those who are not diabetic and glaucoma may result from rubeosis when small vessels form in the angle of the anterior chamber. The most serious form of diabetic eye disease, however, affects the retina and vitreous. The characteristic retinal lesions are microaneurysms and blot haemorrhages with hard and soft exudates and the retinal veins are usually dilated and irregular. If this progresses, small new vessels may arise with fibrosis. This can result in retinitis proliferans with severe impairment of vision and may also lead to vitreous haemorrhages, adding to visual loss, although this aspect may recover.

Although not conclusively shown to improve prognosis, it is reasonable to keep patients with diabetic eye disease under particularly good control. Cataracts and glaucoma respond to the usual measures but retinopathy is a far more serious problem. Clofibrate speeds the resolution of exudates, but does not improve vision. Pituitary ablation may retard new vessel formation and venous dilatation, but its ultimate effect in preserving sight is still not definitely known. The most hopeful form of treatment at the moment is laser photocoagulation of new vessels, which may prevent retinitis proliferans and vitreous haemorrhages. Where vitreous haemorrhage has occurred and does not clear, vitrectomy may result in recovery of vision. In spite of these measures, diabetic eye disease remains a significant cause of blindness in the United Kingdom.

Transient visual loss

Complete loss of vision in one or both eyes, lasting for only a short period is known as amaurosis fugax. It results from a temporary reduction of the retinal arterial supply. This may occur with any episode of systemic hypotension, such as during cardiac arrhythmia, iatrogenic postural hypotension or a simple vaso-vagal episode. In such cases bilateral visual loss frequently occurs but, if retinal perfusion is reduced in one eye, such as from increased intraocular pressure, it may be unilateral.

The major cause of transient unilateral visual loss is emboli passing through and occluding the ophthalmic, central retinal and retinal branch arteries. The emboli may be composed of platelet aggregates or cholesterol crystals and arise from two main sources, the heart and the carotid arteries. Occasionally, emboli may actually be seen passing through the retinal circulation. Cholesterol emboli are bright and refractile and may leave an area of sheathing of the artery they have traversed. Platelet emboli are more usually detected by an interruption of a column of blood within an artery. Emboli from the heart may form during episodes of paroxysmal arrhythmia such as supraventricular tachycardia or within an atrium affected by atrial fibrillation. They may arise from abnormal valves, either congenital, such as bicuspid aortic valves or prolapsing mitral valve leaflet, valves damaged by rheumatic fever or bacterial endocarditis, or prosthetic valves. Emboli may originate from mural thrombus in the weeks following a myocardial infarct, or from the thrombus contained within a subsequent left ventricular aneurysm. Patients with mitral valve leaflet prolapse, left ventricular aneurysm and rheumatic heart disease are, of course, also more prone to paroxysmal arrhythmia.

Investigation of patients with amaurosis fugax and a history or physical signs suggesting cardiac abnormalities, including all younger patients with amaurosis fugax, should include, as well as routine radiography and electrocardiography, an echocardiogram and 24-h e.c.g. recordings. In the older age groups emboli more commonly arise from atheromatous plaques in the common and internal carotid arteries. These may be detected as bruits over the arteries, but this is not always the case and carotid arteriography is the investigation of choice.

The significance of amaurosis fugax is not so much the possibility of permanent loss of vision, which is not common, but that such patients are at risk from cerebral embolism and infarction. It is important, therefore, to eliminate the formation of emboli if possible. Cardiac sources will require specific treatment such as drug treatment of arrhythmia and surgery to damaged valves and ventricular aneurysms. Carotid atheromatous plaques are frequently accessible to surgery by endarterectomy. However, sometimes it is not possible to eliminate entirely the risk of embolus formation, and therapy directed primarily at preventing formation is required. In most patients with cardiac emboli and in all in whom there is a history of cerebral embolism, full anticoagulation with warfarin is required. However, platelet embolus formation within the carotid artery has been shown to be inhibited with a small dose of aspirin and trials are in progress to determine whether sulphinpyrazone and dipyridamole are equally as effective.

The visual disturbance of migraine is usually characteristic fortification spectra and shimmering lights warning of the onset of an attack, but occasionally the aura may consist of an homonymous hemianopia lasting a few minutes. Rarely, this aura may occur regularly without being followed by a headache, resulting in diagnostic confusion. The limited duration of these episodes, however, gives a clue as to their aetiology.

Haematological disorders

Any haematological disorder which increases blood viscosity, such as leukaemia, thrombocythaemia, polycythaemia and dysproteinaemia, may cause retinal artery and vein occlusions and may encourage the formation of emboli resulting in amaurosis fugax. More specific ocular abnormalities occur in pernicious anaemia, which may result in a swollen optic disc with a central scotoma and decreased visual acuity, and the various forms of sickle cell disease which may cause retinitis proliferans, vitreous haemorrhages and retinal detachments. Prophylactic laser photocoagulation may reduce the risk of these complications.

Endocrine disorders

Pituitary tumours

The majority of intrinsic pituitary tumours are slowly growing chromophobe adenomas. These can cause endocrine disturbances so insidiously that the first symptom noticed by the patient is visual loss resulting from the bitemporal hemianopia of chiasmal compression and they will initially present to the ophthalmologist. When a bitemporal hemianopia presents, a careful history of possible symptoms of hypopituitarism (with *direct* questions concerning impotence and loss of libido) should be taken. The patient will then require admission for a full radiological and endocrine work-up before surgery or radiotherapy, or both. The same considerations apply to any other tumour causing chiasmal compression, such as hypothalamic secondaries and craniopharyngioma. It should be noted that any patient with a suspected pituitary tumour should have a booster dose of steroids before any general anaesthetic, although the endocrinologists should be informed in case this interferes with their investigations.

Thyroid eye disease

Graves' disease is accompanied typically by the eye signs of upper lid retraction and swelling and unilateral or bilateral exophthalmos. More severe cases may show chemosis, corneal abrasions as a result of inability to close the eyelids, ophthalmoplegia and diplopia (usually on upward gaze). Very severe cases may lead to visual loss as a result of compression of the optic nerve from the increased pressure within the orbits. Such cases are medical emergencies and require immediate treatment with high doses of steroids, with or without azathioprine; if there is no improvement or vision continues to deteriorate, orbital decompression must be performed. Plasmaphoresis has been used in these conditions with success, but is still experimental.

While most cases of thyroid eye disease develop concurrently with clinical and biochemical hypothyroidism, some cases occur in euthyroid patients with normal free thyroxine concentrations. However, more than half such patients will show a flat TSH response to i.v. TRH which is characteristic of hyperthyroidism and many patients will develop overt hyperthyroidism in the future. In some cases, thyroid eye disease occurs after hyperthyroidism has been brought under control and it may be precipitated if the patient is rendered hypothyroid. The mechanism of thyroid eye disease is believed to be mediated by immunoglobulins, but routine tests for thyroid-stimulating immunoglobulins are not yet generally available. However, antithyroid antibodies, which can be measured in most hospitals, are also frequently present in such cases.

Abnormalities of calcium metabolism may be suspected from ocular examination. Hypercalcaemia can cause deposits of calcium at the lateral margins of the cornea, while prolonged hypocalcaemia may cause cataracts and papilloedema as part of the syndrome of bening intracranial hypertension.

DRUGS

Many drugs can affect the eye. Some of these have already been mentioned, but the most commonly used drugs with the most serious ocular side-effects are corticosteroids, chloroquine and ethambutol. Use of local and systemic steroids can cause cataracts as well as increasing intraocular pressure and precipitating glaucoma. As mentioned above, applying local steroids to herpetic keratitis may make the condition worse and result in permanent corneal scarring. Chloroquine is deposited in melanin-containing tissues including the choroid, and when used for prolonged periods can cause a toxic retinopathy with a characteristic Bull's Eye appearance at the macula. Once visual loss has occurred it is usually irreversible and use of this drug for extended periods of treatment, such as in rheumatoid arthritis and systemic lupus erythomatosus should be accompanied by regular tests of visual acuity and colour vision. Such checks are also necessary when treating tuberculosis with ethambutol as this drug can cause toxic optic neuropathy. The usual regime of 15 mg kg^{-1} daily is considered unlikely to cause visual loss, but cases have been recorded at this dose, and although vision frequently improves after the drug has been withdrawn, this is not always the case.

Although this paper has reviewed only some of the more important systemic disorders affecting the eye, it has emphasized particularly that examination of the eye is a revealing and essential part of the general examination of any patient.

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Walsh, F. B., and Hoyt, W. F. (1969). *Clinical Neuro-Ophthalmology* (3rd edn, vols 1, 2, 3). Baltimore: Williams and Wilkins Co.

Br. J. Anaesth. (1980), **52**, 705

CORRESPONDENCE

OCCLUSION OF DORSALIS PEDIS ARTERY

Sir,—I was interested to read the paper by Husum, Palm and Eriksen (1979) on the effects of occlusion of the dorsalis pedis artery, but dismayed that they see fit to condemn its routine cannulation.

For the past 7 years I have, if possible, used a cannula in the dorsalis pedis artery to monitor arterial pressure and gases in patients undergoing neurosurgical operations. During that time I have cannulated this artery in more than 500 patients ranging in age from 18 months to 80 years. In some of these I have used the same artery on more than one occasion and have not seen any clinical evidence of compromise to the circulation.

It is right and proper that the effects of the techniques that we use should be investigated and the results published. All the choices we make are compromises reached by weighing up the relative advantages and disadvantages of the alternatives. I hope that, if the occasion arises, my anaesthetist will use my dorsalis pedis artery in preference to my radial, for if a disaster should occur I would rather lose toes than fingers.

David Hurter
Kent

REFERENCE

Husum, B., Palm, T., and Eriksen, J. (1979). Percutaneous cannulation of the dorsalis pedis artery. *Br. J. Anaesth.*, **51**, 1055.

TORSION OF THE INNER TUBE

Sir,—I wish to report a hazard discovered during the use of a Bain type coaxial anaesthetic circuit, manufactured by Messrs Penlon Limited (Bain and Spoerel, 1972). This fault is, I believe, hitherto unreported in the literature.

Following connection of the system to the fresh gas outlet of an anaesthetic machine, it was noted that no fresh gas was being delivered at the patient end connector. On inspection of the valve and tubing it was discovered that the inner fresh gas supply tube of the coaxial system had become twisted (approximately eight times) along its longitudinal axis, resulting in occlusion of the inner tube. The fault was easily corrected by dismantling the system and untwisting the tube. I believe that this failure was caused by the usual "twist and push" action used to fit the patient end connector to the mask or catheter mount, the outer tube rotating slightly on the end connector each time, allowing the torsion of the inner tube to increase, leading eventually to occlusion as described.

I have discussed this fault with the manufacturers, who recognize this potential hazard, and recommend that in addition to confirming gas flow and inspecting the inner tube, the coaxial tubing assembly should be replaced at regular intervals, as continued exposure to anaesthetic agents softens the material of the inner tube, rendering it more susceptible to occlusion as a result of torsion.

I would suggest that instead of incurring repeated expense in such regular total replacement of both tubes, the inner fresh gas tube should be manufactured from a textile-reinforced material, which, by its nature, would resist torsion and occlusion, even after softening as a result of exposure to anaesthetic agents.

Michael S. Inglis
Poole, Dorset

REFERENCE

Bain, J. A., and Spoerel, W. E., (1972). A streamlined anaesthetic system. *Can. Anaesth. Soc. J.*, **19**, 426.

Sir,—The hazard caused by excessive twisting of the inner tube is specifically referred to in the "pre-use safety checks" included in our Data sheet CC178PS which is included with all coaxial circuits when supplied.

We fully agree that the reinforced tubing suggested by Dr Inglis would have inherent safety advantages and we will endeavour to find suitable tubing. Dr Inglis was kind enough to send us a sample of p.v.c. compressed air hose to illustrate his proposal, but unfortunately this tubing would not itself be suitable as it is not antistatic and we know from experience that the plasticized p.v.c. material from which it is made can become brittle after prolonged exposure to halothane.

We feel it necessary to point out that the outer polythene tube does not have an indefinite life. Small cracks are liable to develop in this tubing, which may result in undesirable leaks although these are clearly less critical than the cutting off of fresh gas supply by the collapse of the inner tube. It is therefore important that users recognize that neither the inner or outer tube of the coaxial circuit is to be considered permanent and that they require frequent inspection.

It would be useful to collate and analyse the experience of anaesthetists concerning the safe life of these assemblies, and if users would care to send details of their experience to the undersigned, we would be pleased to see if these could lead to recommendations concerning a safe working life which could be submitted for publication in these columns.

B. R. Sugg
Technical Director,
Penlon Ltd, Abingdon

APPARATUS FAILURE—CAUSE FOR CONCERN

Sir,—An issue of your journal was devoted to the hazards of anaesthesia and in that Editorial, Hull and Norman (1978) drew particular attention to the danger of any change in the usual practice of anaesthesia. Since the publication of that issue we have experienced three serious apparatus faults and these problems occurred when changes were made in our usual practice of anaesthesia.

In the first incident a new Lack co-axial breathing circuit (Lack, 1976a, b) was brought into use after examination in accordance with the accompanying leaflet. During the course of a discussion on the characteristics of the circuit, we realized that it was wrongly manufactured, although it appeared to function normally. The faulty circuit was so constructed that the inner expiratory tube, which should have been connected to the expiratory (exhaust) valve, was in fact connected to the reservoir bag. This arrangement placed the whole of the circuit tubing (1.5 m long × 28 m^{-3} diameter) and the reservoir bag on the patient's side of the expiratory valve and converted it to deadspace. The exhaust outlet assembly is a robust metal construction, an integral part of which is the right-angled connection linking the inner expiratory tube to the expiratory valve. In the faulty circuit, this right-angled connection turned down to the reservoir bag instead of up to the exhaust valve, but this was only visible when looking down the fresh gas inlet taper of the circuit. A test of the integrity of the circuit is to disconnect the inner and outer tubes at the patient end, and exhale down the inner expiratory tube with the expiratory valve open. The properly assembled system directs the expired air to atmosphere via the valve. In the faulty system expiration distends the bag. Our recognition of this fault led to the issue of a recent hazard warning (Ref. DHSS 79/18).

In the second incident, the cuff of a nasotracheal tube collapsed inward and obstructed a patient's airway. A change in the usual routine of preparing these tubes had been instituted, unknown to the anaesthetist. They were being packed for autoclaving with the non-return inflating valve in place on the end of the pilot tube, although the cuff was not inflated. It seemed that the small amount of air trapped after insertion of the valve, expanded by heat and aided by the negative pressure in the autoclaving cycle was enough to weaken the wall of the tube. On cuff inflation the weakened tube wall tends to collapse inward and occlude the lumen, particularly when there is a restriction to the outward expansion of the cuff when the tube is in the trachea. Examination of several similar tubes revealed the same fault to a varying degree (Warne Surgical Products re-usable cuffed nasotracheal tubes). Subsequent testing at the W.S.P. laboratories confirmed these findings. The wall of the tube is reinforced by a nylon spiral and at an autoclaving temperature of 134 °C the nylon becomes very soft and deforms easily. After cooling it may remain deformed and weak. The manufacturers now recommend that an autoclaving temperature of 120 °C should not be exceeded (D. Emm, W.S.P., personal communication). Nevertheless it would seem wise not to autoclave endotracheal tubes with non-return inflating valves *in situ*.

In the third incident, the oxygen supply failed during the administration of a general anaesthetic. A Boyle's machine supplied by a flexible pipeline from a wall-mounted connection was in use. The pipeline was suspended over a gantry 2.15 m high to avoid damage to it. The cause of the failure in the oxygen supply was a kink in the pipeline immediately adjacent to the permanent connection point on the back of the Boyle's machine. Neither the anaesthetic machine nor the flexible pipeline had been moved at the time of the incident; the pipeline was not at full stretch. Subsequent examination revealed that the nylon reinforcement of the pipeline was damaged at this point—from wear and tear—although this was not evident on external inspection. Presumably the tensions generated by an unsatisfactory "hang" of the pipeline caused it to kink at this weak point. The pipeline was the subject of a regular maintenance contract. A similar incident could occur whenever a pipeline approaches an anaesthetic machine from above, as it must turn through 180° to the permanent connection point on the back of the machine. In order to avoid acute angulation, there should always be an adequate length of pipeline, never at full stretch, which should curve naturally away from the permanent connection point. Consideration should perhaps be given to strengthening pipelines at this point.

Fortunately, none of these incidents resulted in harm to patients.

J. Muir
R. Davidson-Lamb
Aberdeen

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—— (1976b). Pollution control by co-axial circuits. *Anaesthesia*, **31**, 561.

MINAXOLONE AND MALIGNANT HYPERTHERMIA

Sir,—Althesin has been shown to block initiation of the malignant hyperthermia syndrome by halothane in MHS swine (Hall, Trim and Woolf, 1972; Harrison, 1973), and recommended for use in human subjects susceptible to the condition (Honda et al., 1977).

It was of interest, therefore, to ascertain whether minaxolone, the water-soluble steroid anaesthetic (Aveling et al., 1979; McNeill, Clarke and Dundee, 1979) possessed similar properties.

We report here the results of our investigation in four MHS swine of the effects of continuous infusion of minaxolone on the initiation of the MH syndrome by halothane. The experimental programme used was similato that described previously (Harrison, 1973) with modificartion which included:

(1) Direct arterial pressure monitoring via femoral artery cannulation.
(2) Use of a cerebral function monitor.
(3) GLC assay of blood concentrations of minaxolone during the experiment.

Dosage of minaxolone was as follows: induction—1.4–2 mg kg^{-1}; maintenance infusion—40–100 μg kg^{-1} min^{-1}; total dose (45–60 min)—4–6 mg kg^{-1}.

Intravenous concentrations of minaxolone varied from 0.66 to 1.55 μg ml^{-1} in most, and 2.84 μg ml^{-1} in one pig where the infusion rate was greatly increased in an attempt to abort the onset of MH.

Although minaxolone itself did not provoke the onset of the syndrome, in all four experiments it failed to block initiation of the MH syndrome in response to the administration of halothane, the syndrome being well established within 20 min of exposure in each case.

We cannot as yet define the role, if any, of cremophor (the solvent for Althesin) in these contrasting actions of Althesin and minaxolone.

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4-AMINOPYRIDINE FAILS TO INDUCE PORCINE MALIGNANT HYPERTHERMIA

Sir,—4-Aminopyridine (4-AP) has been introduced recently to clinical practice for the antagonism of neuromuscular blockade produced either by curare-like agents (Stoyanov et al., 1976), or antibiotics (Booij, Miller and Crul, 1978), and for the treatment of myasthenia gravis (Lundh, Nilsson and Rosen, 1979), and the Eaton–Lambert syndrome (Lundh, Nilsson and Rosen, 1977). 4-AP facilitates neuromuscular transmission by a pre-synaptic effect on the motor nerve terminal in which both the spontaneous and the evoked output of acetylcholine is increased, and also by a direct effect on muscle to increase contractility (Bowman, Khan and Savage, 1977). The mode of action of 4-AP is thought to be an increase in the intracellular Ca^{2+} concentration either as a result of blockade of the potassium channel in the cell membrane with prolongation of the action potential (Molgo, Lemeignan and Lechat, 1977), or by a direct effect on the calcium channel in the membrane (Lundh and Thesleff, 1977). There are, therefore, good grounds for suggesting that 4-AP may trigger porcine malignant hyperthermia (MH), since this syndrome is caused by an increase in the Ca^{2+} concentration within the striated muscle cell. This contention is supported by studies which have shown that the effects of 4-AP on striated muscle are antagonized by dantrolene (Bowman, Khan and Savage, 1977) and Mg^{2+} (Marshall, Lambert and Durant, 1979), both of which have been used successfully to treat porcine MH (Hall, Lucke and Lister, 1980).

We have investigated the effects of the administration of 4-AP in four MH-susceptible Pietrain pigs, anaesthetized with increments of thiopentone, the lungs being ventilated artificially with nitrous oxide in oxygen. 4-AP was administered i.v. in a total dose of 3–4 mg kg^{-1} body weight. In a preliminary experiment we demonstrated that 4-AP had a marked direct effect on the muscle at this dose as it was possible to reduce only partially the coarse muscle twitching by the administration of large doses of pancuronium. The ability of 4-AP to trigger MH was assessed by frequent estimations of arterial blood-gas tensions, muscle temperature, plasma potassium and blood lactate concentrations for 1–2 h. 4-AP failed to induce MH in all the pigs studied and their susceptibility was proven at the end of the experiment by ventilating with 1% halothane.

The inability of 4-AP to trigger porcine MH suggests that this compound is unlikely to induce MH in susceptible patients. The dose of 4-AP used in this study was 10 times greater than the 0.35 mg kg^{-1} body weight recommended for use with neostigmine for the antagonism of neuromuscular blockade in man) Miller, 1979). Furthermore, the results indicate that porcine MH cannot be induced by a compound the effect of which is mediated, at least partly, by a direct action on the muscle membrane to increase the intracellular Ca^{2+} concentration. This suggests that the recent emphasis on the sarcolemma or sarcolemma–sarcoplasmic reticulum junction as the site of the primary defect in MH may not be valid.

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ACKNOWLEDGEMENTS

We thank Professor W. C. Bowman for helpful advice, and the Muscular Dystrophy Group of Great Britain for financial support.

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RATE OF INJECTION AND SPREAD OF EXTRADURAL SOLUTIONS

Sir,—We were most interested to see the paper on lumbar extradural injection pressures in pregnant women (Husemeyer and White, 1980), since it confirmed our findings of some years ago (Burn, Guyer and Langdon, 1973). Using epidurograms to study the spread of solutions in the extradural space we too concluded that the rate of injection did not correlate with the degree of spread. Incidentally, Nishimura, Kitahara and Kusakabe (1959) reached the same conclusion using yet another technique employing radioisotope tracers.

The lack of correlation between the rates of injection and the injection pressures reported by Husemeyer and White is surely because the subjects were all young people and relatively small volumes were used. As the authors rightly say "Injection pressures may therefore depend as much on the rate of leakage as on the rate of injection." In our series, volumes of 20 and 40 ml were used with an age range 21–69 yr; our experience confirmed the findings of Erdemir, Soper and Sweet (1965) and Usubiaga, Wikinski and Usubiaga (1967) that, under such circumstances, rapid injections (1–2 ml s^{-1}) can produce high pressures resulting in unpleasant and possibly even hazardous effects.

Our conclusion was that, as rapid injections appeared to confer no clinical benefit, they should not be used.

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EFFECTS OF INTRAOPERATIVE NEFOPAM (ACUPAN)

Sir,—Nefopam is a novel analgesic which appears to have no respiratory depressant effects. It does, however, cause an increase in heart rate and arterial pressure, and also sweating and flushing. A simple study was carried out to ascertain whether these effects would also be seen when nefopam is given to patients anaesthetized with halothane. Thirty-one patients were studied, most of whom were undergoing minor general surgical procedures, hysterectomy or tubal ligation. Nefopam was given at a time when effects of surgical stimulation on heart rate and arterial pressure would be minimal.

In 17 patients, breathing was spontaneous; 15 of these showed an increase in heart rate (range 4–32 beat min^{-1}) and 14 showed an increase in arterial pressure (range 5.1–35.2 mm Hg). In the 14 artificially ventilated patients, seven showed an increase in heart rate (range 8–72 beat min^{-1}) and 12 an increase in arterial pressure (range 5.1–35.2 mm Hg). Two patients sweated and six were flushed. In three of these patients, these effects were not observed until the patient was in the recovery room. One patient showed an increase in heart rate from 88 to 160 beat min^{-1} during operation and after operation her arterial pressure readings were 160/110 and 145/115 mm Hg. She was not hypertensive before her operation.

Insufficient patients were studied to ascertain whether there was any association between particular anaesthetic drugs and these changes of heart rate and arterial pressure. It is suggested that caution should be exercised in the use of nefopam during the course of an anaesthetic.

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ARRHYTHMIAS AND THE CAROTID ARTERY

Sir,—I have read with interest two letters in the past year in which the authors describe severe cardiac arrhythmia as a result of carotid artery palpation. Amaranath, Kirilcuk and Leon-Ruiz (1978) described multiple deformed QRS complexes which occurred while routinely palpating the carotid artery during hip replacement. Sprigge and Oakley (1979) recorded a case of ventricular fibrillation following palpation of the carotid artery before cannulation of the internal jugular vein.

These reports were of concern in a department which undertakes a considerable number of general anaesthetics for carotid angiography. At Atkinson Morley's Hospital, carotid angiography is carried out following direct puncture of the carotid artery and this procedure necessitates handling of the carotid vessels both during cannulation and after de-cannulation to ensure haemostasis. It was decided, therefore, to monitor these patients continuously with an electrocardiograph and to record any abnormality produced.

The patients were in a wide age group, from young adults to the very elderly. They were being investigated for a variety of neurological conditions, but most commonly following subarachnoid haemorrhage. Patients less than 65 years of age were premedicated with hyoscine 0.3 mg, those older than 65 with atropine 0.4 mg i.m. Anaesthesia was induced with thiopentone, tracheal intubation followed relaxation with suxamethonium and IPPV continued using tubocurarine as the muscle relaxant. Anaesthesia was maintained with nitrous oxide, oxygen and either small doses of fentanyl or halothane 0.25–0.5%.

More than 100 patients have now been monitored and no cardiac arrhythmia has occurred. Thus, it would seem that prolonged manipulation and handling of the carotid artery is not usually accompanied by cardiac arrhythmia. This does not detract from the finding that, in an occasional patient, perhaps especially those with pre-existing cardiovascular disease, a serious abnormality of cardiac rhythm may occur. However, it would seem unnecessary, for example, to monitor the e.c.g. routinely in every patient requiring cannulation of the internal jugular vein.

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BOOK REVIEWS

Self-Assessment of Current Knowledge in Anesthesiology, 2nd edn. By David L. Trickey. Published (1980) by Medical Examination Publishing Co. Inc., New York. Pp. 200. Price $14.00.

The trouble with multiple-choice questions is not that they exist or that they are published, but that clinicians look on them as an evil to be faced only before sitting examinations. This is a pity, since many of us are missing an enjoyable and easy method of keeping abreast of advances in our chosen speciality.

This volume contains 807 multiple-choice questions with explanatory answers and many useful references. It is divided very well into seven chapters on different aspects of anaesthesia such as pulmonary medicine and anaesthesia; obstetric, regional and neonatal anaesthesia; hepatic and renal physiology, medicine and anaesthesia. Case histories are included to give the reader an opportunity to choose the most appropriate course of action in a particular situation. The questions are interesting and revealing, the references are recent and appropriate, and the answers are clear and accurate. The only criticism might be that only one answer to each question is correct.

Fortunately, the author states in the preface that the reader should not be alarmed at how many of the questions he answers incorrectly. The aim is not to achieve a high score but to learn and to keep abreast of current advances. This volume is a significant contribution towards the goal of continuing education for clinicians. It is highly recommended.

W. S. Nimmo

Pain. Association for Research in Nervous and Mental Disease, Volume 58. Edited by John J. Bonica. Published (1980) by Raven Press, New York. Pp. 391; illustrated; indexed. Price $47.60.

This volume contains the proceedings of the scientific sessions held during the 58th Annual Meeting of the Association for Research in Nervous and Mental Disease which took place in mid-1979.

The book is divided into two parts, the first dealing with the basic aspects of pain under three headings: anatomy and physiology of peripheral, spinal and brainstem systems; psychological and psychiatric aspects of pain; modulation of pain, with contributions from authorities such as Melzack, Wall and Snyder. The second section of the book contains papers on specific clinical aspects of pain control including the role of the psychiatrist, and the treatment of headache, causalgia, cancer and low-back pain; the authors include Mersky, Sweet and Bonica.

The anatomical and physiological papers provide an excellent review of knowledge concerning the pathways and mechanisms of pain up to the time of the meeting and are a fruitful source of reference. It is, however, indicative of the pace at which investigation into pain is progressing that portions of the work have been superseded by more recent findings.

The clinical papers are rather disappointing for many of the more recent innovations in pain therapy are not mentioned. In Bonica's paper on cancer pain, although some 87 references are cited, there are one or two notable omissions such as the papers by Robert Maher on the use of intrathecal neurolytic agents. Papers by Tasker on deafferentation and causalgia and by Loeser on low-back pain are made remarkable by what is omitted rather than by what is included. There is a sound presentation from Sweet on central lesions in pain relief and an excellent cameo by Mersky on the role of the psychiatrist.

Overall, the volume provides a useful source of reference for the scientific basis of pain and for some clinical areas. However, it is difficult to determine to whom this book will appeal as it is insufficiently comprehensive or contemporary for those with a specialist interest in pain and yet too detailed and patchy for the non-specialist. As regards both editing and production, the volume is well presented. Above all, the inclusion of the discussions at the end of each section gives the reader the chance to learn a great deal about the participants which is, at times, more interesting than the foregoing papers.

Keith Budd

Renal Function in Anaesthesia and Surgery. By D. R. Bevan. Published by Academic Press. Pp. 239; illustrated; indexed. Price £15.20.

Although renal function during anaesthesia and surgery is of less immediate importance to the anaesthetist than is the function of the heart and lungs, there has been a recent burgeoning of interest in the subject. There are probably several reasons for this. The discovery of the specific nephrotoxic effect of methoxyflurane stimulated further consideration of the whole subject of renal failure following surgery, whilst increasing numbers of patients with poor, or even absent, renal function are being presented for surgery.

This book will be widely and deservedly welcomed as a comprehensive and extremely readable account of a difficult subject. As a single-author book it represents a remarkable tribute to the diligence of D. R. Bevan, who has himself contributed to the subject, and whose departure from the United Kingdom for Canada represents a real loss to academic anaesthesia in the older country.

Renal Function in Anaesthesia and Surgery is divided into three parts: basic principles (anatomy, physiology and the like) occupy something less than half of the text; the other two sections are on renal function during anaesthesia and surgery, and on renal failure. The last section is, perhaps, the least happy; the chapters in it on the pathenogenesis of renal failure and on the hepato-renal syndrome in particular being less helpful than the rest. It has become customary to state that there are a number of misprints (although the reviewer would be interested to know if there has ever been a book entirely without them). Figure 4.3 might be a little confusing to the neophyte for this reason but the use of "Electric cases" for Elective cases in the last table of the book can do nothing but provide the reader with a good-humoured smile.

These criticisms should not, however, detract from what is, essentially, an excellent contribution to the subject. Doubtless to advise candidates for the final fellowship examination to read it from cover to cover would be to add a further burden to them at an already overburdensome time. Nevertheless, they would find much of value in it, especially about anaesthetizing patients with renal failure. There is, too, a comprehensive list of references for those who wish to go into the subject in greater depth; as is usually the case, however, this is rather less up to date than it might be.

J. E. Utting

Electrocardiography for the Anaesthetist, 4th edn. By W. N. Rollason. Published by Blackwell Scientific Publications. Oxford, Pp. 154; illustrated; indexed. Price £7.85.

Why should the clinical anaesthetist read a book on electrocardiography? First to acquaint himself with the basic principles of the e.c.g. and the general process of pattern recognition in health and cardiac disease. These he can achieve by reading one of the standard primers on electrocardiography. Second, he would wish to be brought up to date on the advances in the application of the electrocardiogram in the preoperative evaluation and peroperative monitoring of the patient with cardiovascular disease. Also he would wish to acquire an understanding of the advances in electrophysiology which are relevant to clinical anaesthetic practice. A book which progresses to a fourth edition must have achieved commercial success; and yet this edition which appears only 5 years after the previous edition, does less than justice to these aims. The appearance and format of the book are attractive and in general the figures are clear. The first 60 pages are devoted to a replication of information which is readily available in a number of simple e.c.g. primers. While this is entirely appropriate as an introduction to the subject, the anaesthetic aspect of the book is a disappointing sequel. The author does little to instruct the clinical anaesthetist in the current approaches to the use of the e.c.g. in evaluation of the patient before operation. Consider the inescapable fact that coronary artery disease and hypertension are the commonest cardiovascular disease states in the population presenting for anaesthesia, and yet the author makes but scant reference to these conditions, the importance of e.c.g. assessment, and the considerable recent literature on their relation to anaesthesia. In particular there is no discussion of the importance of differentiating between subendocardial and transmural ischaemia, of the pros and cons of exercise e.c.g. testing in patients with ischaemic heart disease, of Prinzmetal's variant angina, or of "ST segment matrix mapping" in the detection of regional myocardial ischaemia. These are not esoteric subjects, but important aspects of common diseases and their evaluation before anaesthesia.

The discussion of figure 79 implies that a patient with an arterial pressure of 270/160 may benefit from having his arterial pressure acutely decreased to 100/80 (*sic*) in order to reduce left ventricular strain. Recent evidence would suggest that the high frequency of neurological damage resulting from such an acute decrease of arterial pressure would far outweigh the advantage of reducing LV strain. No reference is made to an expanding knowledge (since 1967) of the electrophysiological effects of anaesthetics and agents which may be used in anaesthesia, nor of their application together with those of His Bundle electrocardiography in the evaluation of atrio-ventricular conduction disturbances.

The reviewer would take issue with the author's interpretation of certain arrhythmias and their importance during anaesthesia. The author, in common with some others, dismisses junctional dysrhythmia as "frequently seen during anaesthesia but appears to have no special significance", and atrial extrasystoles as "common during cardiac surgery and appear to have no special significance". These statements reflect a superficial approach by the author to two types of supraventricular arrhythmia which are certainly common during anaesthesia, but which are most disruptive to cardiac performance and circulatory stability. In another section the author discusses bifascicular block (right bundle branch block associated with left anterior or posterior hemiblock) in a manner which implies that patients with bifascicular block should have a cardiac pacemaker inserted before anaesthesia, yet he does not discuss the evidence in the literature which indicates that pacing is quite unnecessary.

This newest edition of a previously popular book fails to reflect recent advances in the subject and must be considered to be very outdated in many of the concepts which are presented. The discerning anaesthetist with an interest in cardiovascular disease will be very disappointed.

C. Prys-Roberts

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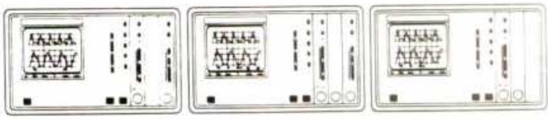

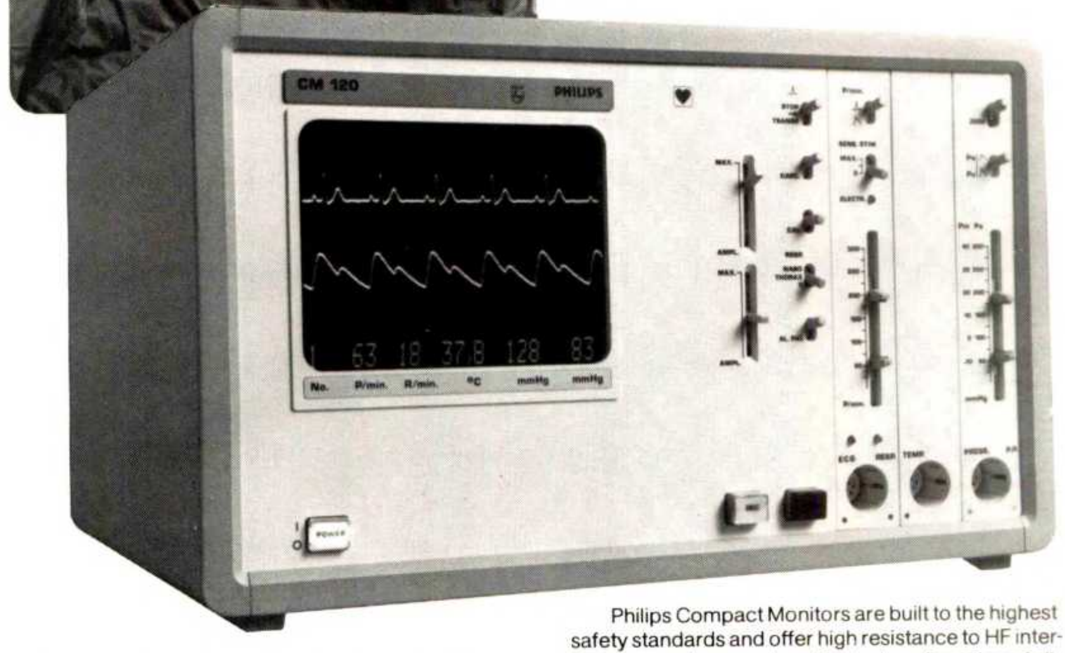

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VOLUME 52, No. 7 *Published monthly* JULY 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27.50, Airmail £50 ISSN 0007-0912

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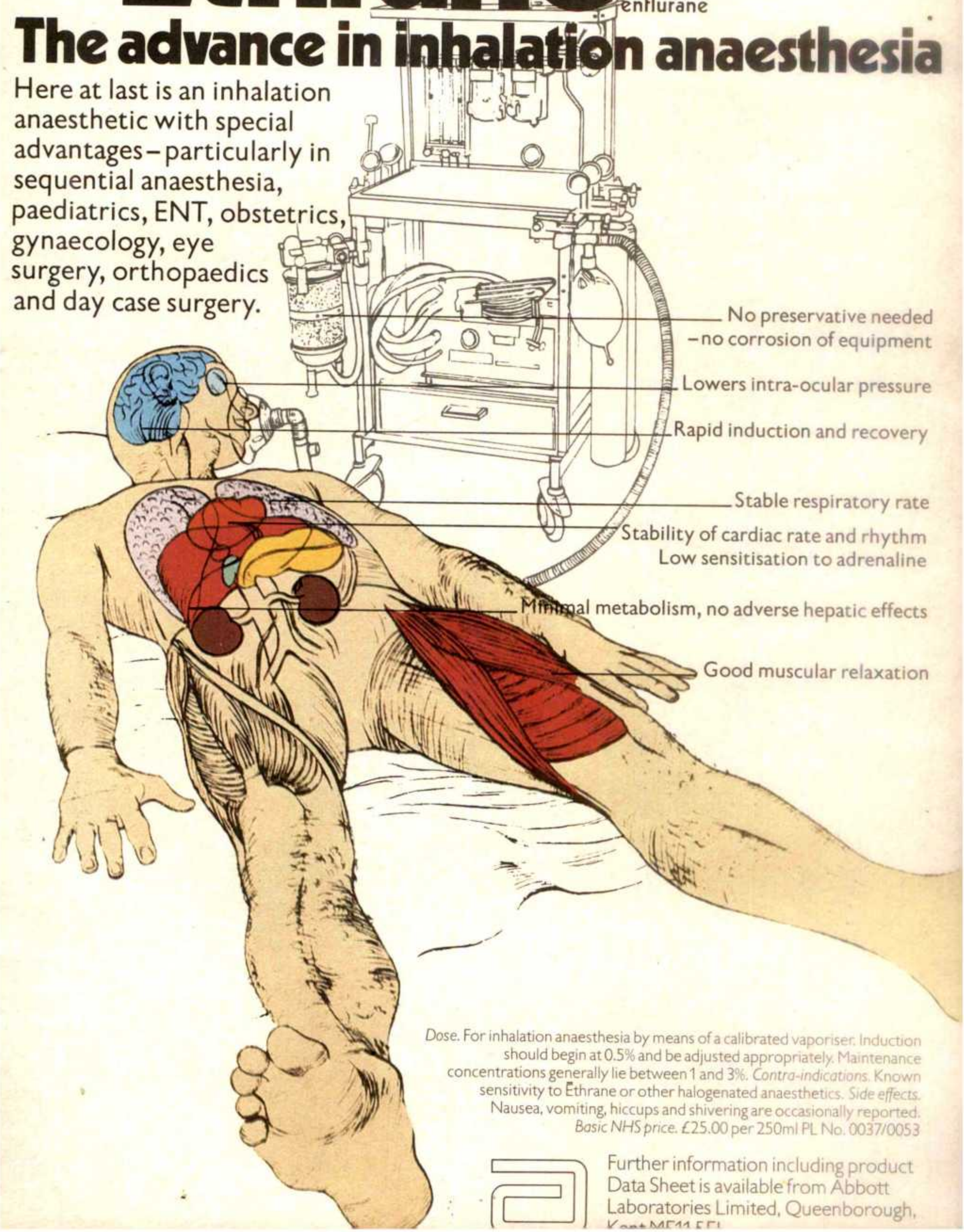

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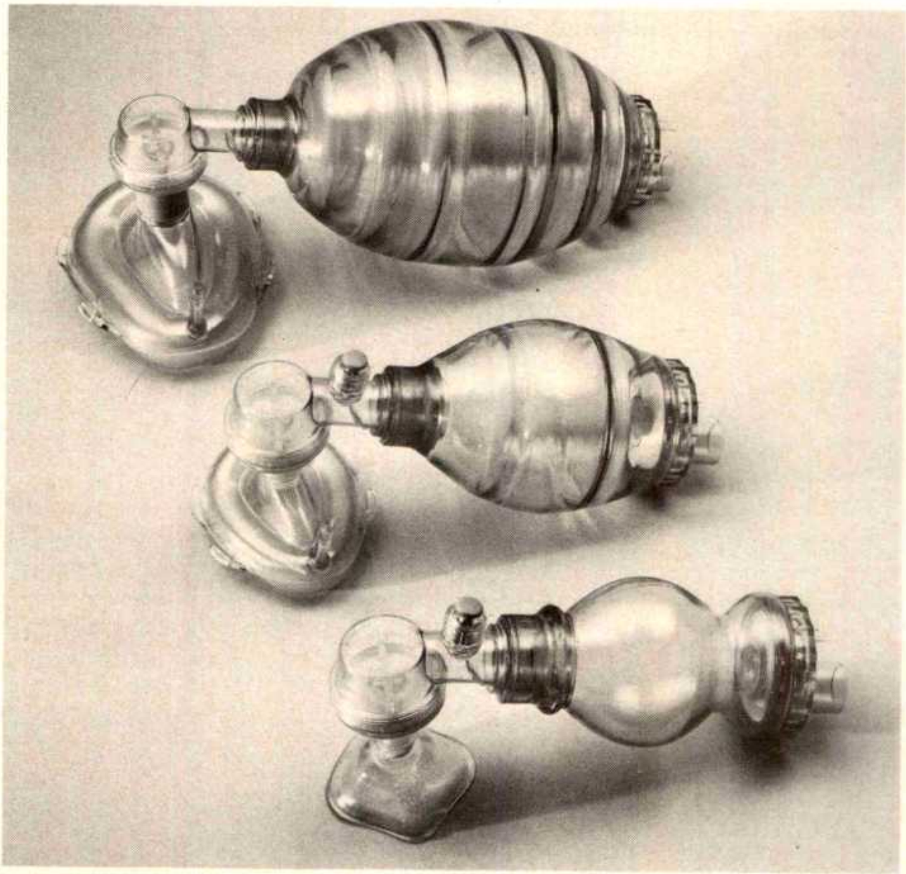

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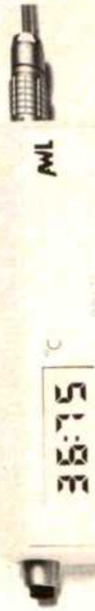

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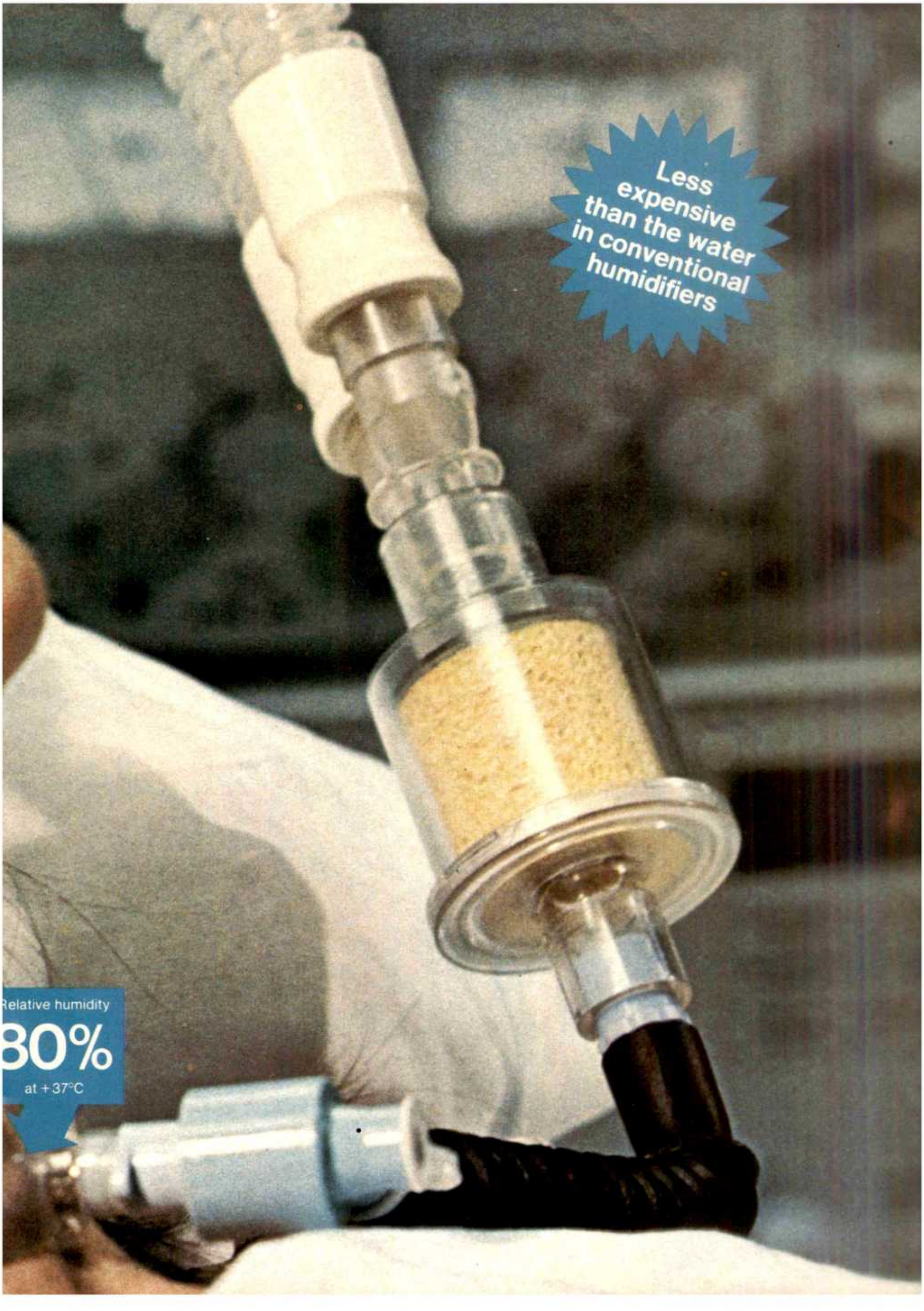
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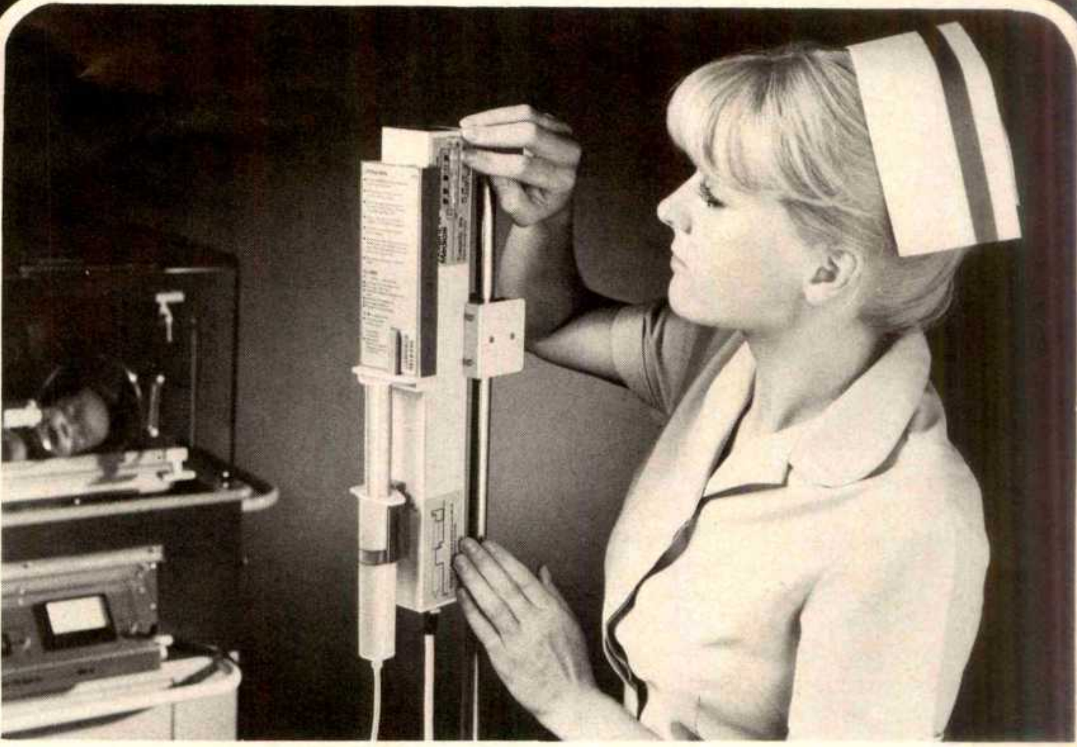

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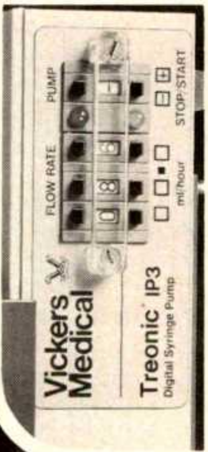

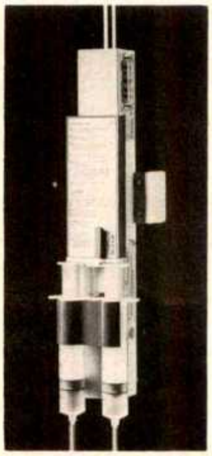

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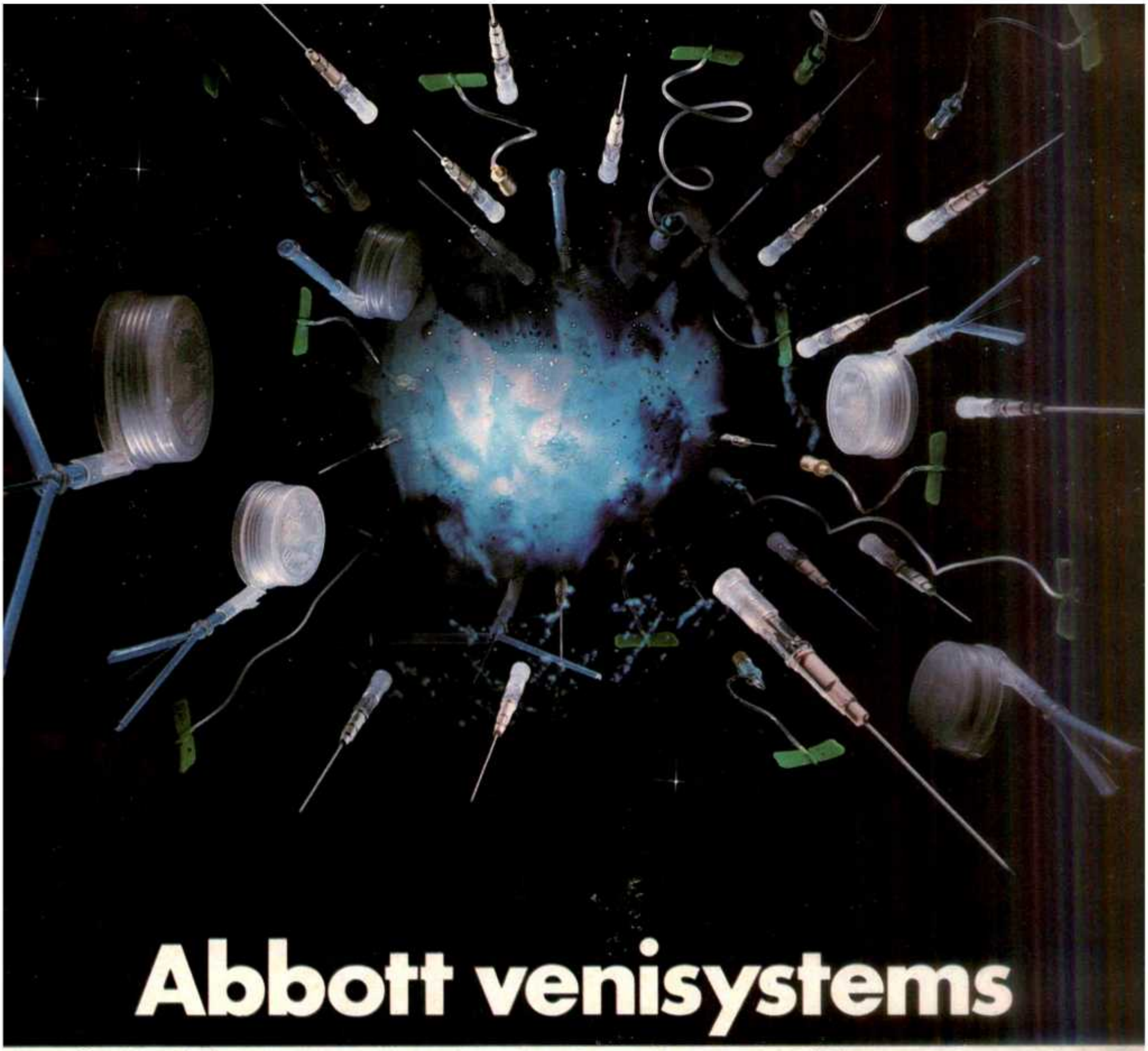

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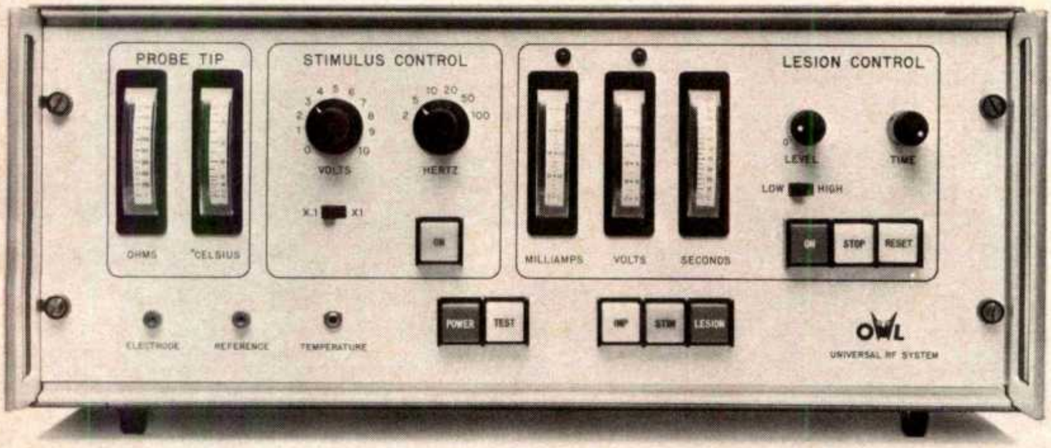

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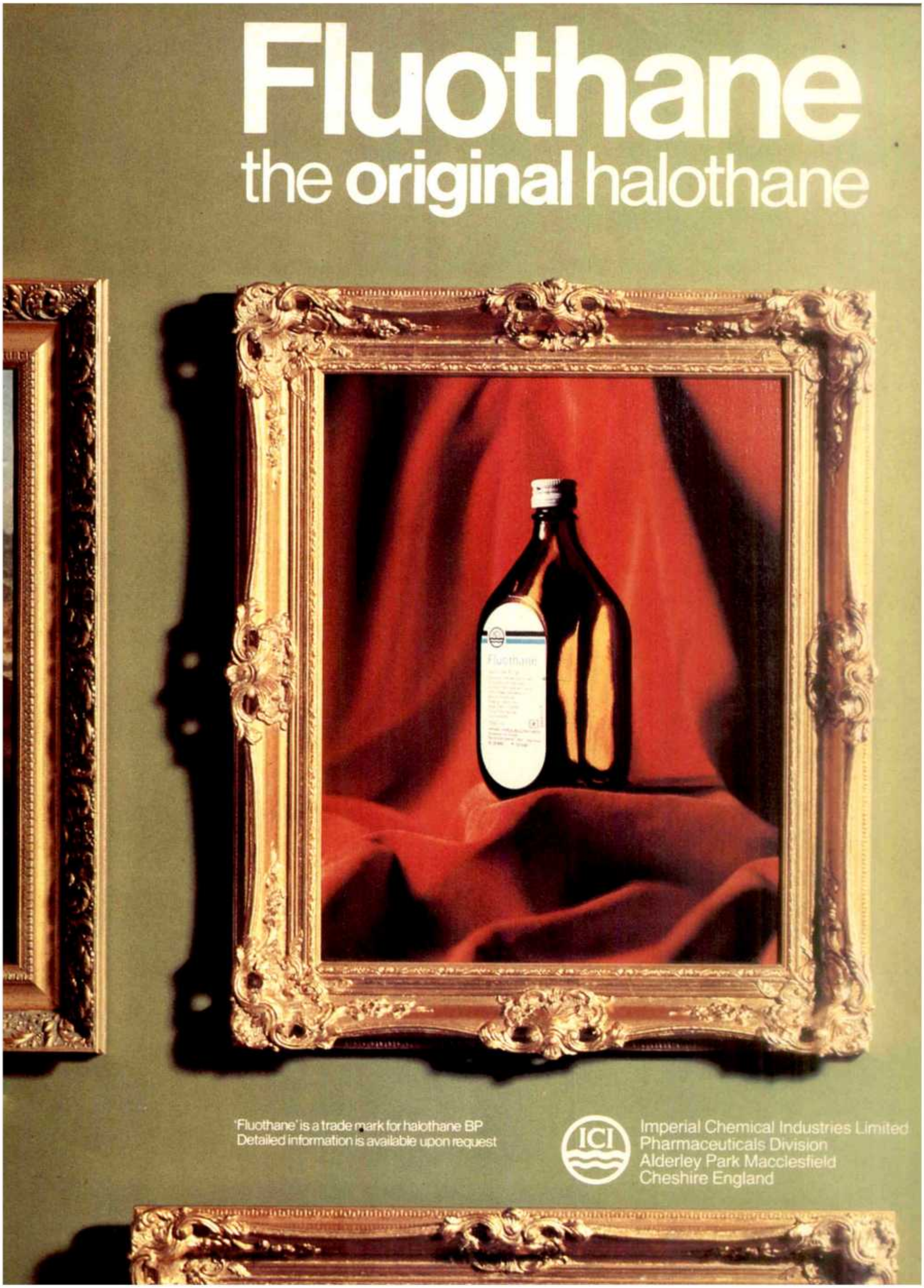

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 8 AUGUST 1980

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EDITORIAL

ANAESTHESIA FOR TERMINATION OF PREGNANCY

Approximately 150 000 operations for termination of pregnancy are carried out annually in the United Kingdom. Seventy-five per cent of procedures are vacuum aspirations under general anaesthesia earlier than 14 weeks' gestation (*Scottish Health Statistics*, 1978). In addition, general anaesthesia is given for evacuation of the uterus following inevitable spontaneous abortion. Abortion remains one of the principal causes of maternal death (Scottish Home and Health Department, 1978; Department of Health and Social Security, 1979), but death attributable to anaesthetic causes during therapeutic abortion is extremely rare, and death caused by haemorrhage in the absence of surgical damage to the uterus is not reported.

It is common practice in anaesthetizing such patients to avoid halothane in view of its myometrial depressant action, demonstrable *in vitro* using both gravid and non-gravid strips of human myometrium (Munson, Maier and Caton, 1969; Munson and Embro, 1977; Naftalin et al., 1977). Other volatile anaesthetic agents, however, have not been subjected to the same intensity of scrutiny.

Munson, Maier and Caton (1969) compared the effects of cyclopropane, nitrous oxide and halothane on isolated non-gravid myometrial strips and concluded that halothane was the most depressant at equivalent anaesthetic concentrations. A similar comparison of enflurane, isoflurane and halothane (Munson and Embro, 1977) found these agents equally depressant at equivalent MAC values. Uterine contractility was significantly decreased at 0.5 MAC, with further depression proportional to dosage. However, the resting uterine tension was not significantly decreased at 0.5 MAC with any of these agents. Comparison of the effect of halothane on gravid and non-gravid myometrial strips has shown that at smaller concentrations ($<1.1\%$) the depressant effect is more marked on gravid myometrium (Naftalin et al., 1977).

Trichloroethylene, which, in some hospitals, has been a popular substitute for halothane in anaesthetizing patients for uterine evacuation, has been subjected to very little investigation. Its previously claimed safety in respect of uterine relaxation was based largely on work carried out in the late 1950's (Talbert et al., 1958). This study comparing the effect of diethyl ether, divinyl ether, cyclopropane, nitrous oxide and trichloroethylene *in vitro* on human myometrial strips concluded that trichloroethylene had little effect on uterine contractility or tonus, while the other agents were potent depressants. However, the duration of exposure of the preparation to the different agents varied and the concentration of the agents was not controlled.

In vitro studies have usually attempted to quantify the effect on myometrial strips of a known concentration of anaesthetic agent in the muscle bath. In the patient, the most feasible measure of anaesthetic tension is the end-tidal or alveolar tension which, in short procedures, will be greater than the tension in uterine tissue. Thus *in vitro* studies may establish the myometrial depressant properties of the volatile anaesthetic agents, but they do not provide a reliable guide to the clinical significance of this effect in the pregnant patient. This can only be established by clinical study.

The effect of halothane in late pregnancy has been investigated extensively. During Caesarean section up to 0.8% halothane could be administered without any increase in blood loss (Moir, 1970). There was, however, a significant decrease in arterial pressure with this concentration, and 0.5% halothane was recommended as a supplement to nitrous oxide anaesthesia.

Evacuation of the uterus following spontaneous incomplete abortion does not lend itself to controlled studies of anaesthesia and blood loss. Only since world-wide changes in abortion laws over the past 10–15 years have controlled investigations of anaesthetic agents on the uterus in early pregnancy been possible. Before this, information relating complications resulting from evacuation of the uterus to the anaesthetic agent used depended on retrospective studies. Batt (1969) studied the frequency of blood transfusion and the administration of oxytocic drugs in a large retrospective series of patients with spontaneous abortion, and concluded that halothane appeared to have no adverse effect compared with non-halothane anaesthesia. There is anecdotal evidence that halothane anaesthesia may be associated with an increased frequency of excessive blood loss at suction termination of pregnancy compared with anaesthesia using nitrous oxide and i.v. supplements (Loung, Buckle and Anderson, 1971), but the overall frequency of excessive bleeding requiring blood transfusion is very small (Diggory, 1969).

The prospective studies of anaesthetic technique and blood loss from the uterus all suffer from the difficulty in measuring blood loss accurately. Methods include haemoglobin dilution techniques and measurement of volume in the suction trap bottle with a correction for estimated amniotic fluid volume, but even these methods may be inaccurate for the relatively small blood losses involved. These prospective studies, however, are the basis for the contention that halothane should be avoided in anaesthetizing patients for evacuation of the uterus.

A widely quoted report (Cullen, Margolis and Eger, 1970) suggested that halothane was associated with an increase in blood loss at vacuum aspiration termination of pregnancy. The total number of patients studied was 87, divided into eight groups with only 10 or 11 patients in each. Several of the anaesthetic techniques utilized would be unlikely in everyday practice. The duration of anaesthesia (25–35 min) was considerably longer than in many countries. The average blood loss for the group anaesthetized with 1% halothane (alveolar concentration) was 283 ml, while a group receiving 0.5% halothane in nitrous oxide suffered a mean loss of 169 ml and the average loss when nitrous oxide was supplemented with an i.v. anaesthetic was 58 ml. Interestingly, no difference was found in blood loss with differing gestational age; this is in conflict with other evidence from both prospective (Moller, Hansen and Mommsen, 1978) and retrospective studies (Dvorak, Truka and Vasacek, 1967; Loung, Buckle and Anderson, 1971), which demonstrated a direct relationship between gestational age and blood loss. (It is now standard practice to avoid vacuum aspiration after 14 weeks' gestation, and induce abortion with prostaglandins.)

In a study by Dunn and colleagues (1973), blood loss following vacuum aspiration termination of pregnancy with trichloroethylene anaesthesia was found to be similar to Cullen's results with halothane anaesthesia. Only seven of 75 patients in the study, however, were anaesthetized with trichloroethylene, and the concentration administered was not reported. Several features of this trial differed from that of Cullen. For example, oxytocin infusion was administered by Cullen while a single dose of ergometrine 0.5 mg was given by Dunn. The relative efficacy of oxytocin and ergometrine in early pregnancy is not established, although they are equally effective in controlling third-stage haemorrhage following delivery (Moodie and Moir, 1976; Moir and Amoa, 1979). There is evidence that the sensitivity of the uterus to oxytocin varies during pregnancy (Theobald, Robards and Suter, 1969).

Isoflurane (Dolan, Eger and Margolis, 1972) and fluroxene (Cullen, Margolis and Eger, 1970) appear to be associated with similar uterine blood loss as occurs with halothane at comparable MAC values. Oats, Vasey and Waldron (1979) have shown a tonic effect of ketamine in the pregnant uterus, but the clinical usefulness of this observation must be tempered by the undesired psychotic effects of this drug when used as the sole anaesthetic. One constant finding of all the quoted prospective studies is that paracervical block is associated with less blood loss than any general anaesthetic technique.

On the present level of knowledge it can be concluded that, in spite of the known influences of different volatile anaesthetics on uterine preparations *in vitro*, there is no clear evidence that a particular technique of general anaesthesia is more or less likely to induce serious haemorrhage during surgical termination of pregnancy. There are two implications of this; first, there is a need for a careful prospective study in which the numbers are sufficient to establish the real risks, if any, of the methods of anaesthesia and the agents available; second, we should consider whether the more elaborate techniques (of i.v. anaesthesia, for example) introduced as a means of avoiding the presumed risks of inhalation methods do not themselves incur new risks. For example, recovery following i.v. anaesthesia may be slower than after a short inhalation anaesthetic (Hannington-Kiff, 1970; Gale, 1976), especially if substantial doses of i.v. agents have been used (Carson, Graham and Dundee, 1975) and this may be important if terminations of pregnancy are performed in outpatients.

I. S. Grant

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ON-LINE Po_2 AND PN_2O ANALYSIS WITH AN *IN VIVO* CATHETER ELECTRODE

W. N. Brooks, C. E. W. Hahn, P. Foëx, P. Maynard and W. J. Albery

SUMMARY

A technique was developed for the *in vivo* determination of Po_2 and PN_2O with a catheter electrode using double-pulse polarography. The method was evaluated in dog studies comparing readings from the electrode with those from a mass spectrometer employing an *in vivo* probe. The oxygen readings obtained from the catheter electrode were also compared with values obtained by conventional blood-gas analysis. Good agreement was observed between the electrode and the mass spectrometer for both Po_2 and PN_2O. Similar agreement was found between the electrode readings and blood-gas analysis for Po_2. In the presence of halothane, the electrode over-read for both Po_2 and PN_2O; a remedy is suggested. The *in vivo* electrode provides an effective, less expensive, alternative to the mass spectrometer for the on-line measurement of Po_2 and PN_2O *in vivo*.

Various *in vivo* Po_2 studies on human adults with catheter polarographic electrodes have been published (Heller et al., 1972; Mindt, 1973; Eberhard, 1975; Sugioka, 1975), although the main thrust of the development and clinical use of these electrodes has been directed towards neonatal intensive care (Rolfe, 1976). The possibility of anaesthetic agents, in particular halothane, interfering with the performance of these electrodes has been emphasized by Bates, Feingold and Gold (1975), following the work of Severinghaus and others (1971). Since at least one commercially available catheter Po_2 electrode has a silver cathode (G. D. Searle & Co.), and since we have shown previously that silver cathodes will polarographically reduce both oxygen and nitrous oxide (Albery et al., 1978; Brooks et al., 1978; Hahn et al., 1979), we have determined if both oxygen and nitrous oxide could be measured *in vivo* on-line in the anaesthetized dog, and if halothane anaesthesia had any effect on the *in vivo* measurements of Po_2 and PN_2O with this type of electrode.

METHODS

Principles of Po_2 and PN_2O measurements

We have shown recently (Albery et al., 1978; Brooks et al., 1978; Hahn et al., 1979) that, although nitrous oxide is electrochemically inactive on platinum or gold cathodes, both nitrous oxide and oxygen can be quantitatively reduced on silver cathodes. Figure 1 shows a typical current–voltage curve for the reduction of an oxygen–nitrous oxide gas mixture using a silver cathode. Two plateaux are observed, corresponding to the reduction of the two gases. By polarizing the electrode at two voltages, −0.65 V and −1.43 V (with respect to the silver/silver chloride electrode), both components of an oxygen–nitrous oxide gas mixture can be measured linearly. However, since nitrogen is generated as a product of nitrous oxide reduction, the electrode cannot be polarized constantly at −1.43 V, as nitrogen bubbles prevent the electrode functioning. This problem can be overcome by applying alternate polarizing voltage pulses of −0.65 V and −1.43 V to the cathode.

Pulsing principle

The technique of pulsing polarographic electrodes for oxygen measurement has been reviewed by Hitchman (1978), although the method is not applied commonly to blood-gas electrodes. The theory of this technique for flat plane membrane-covered electrodes has been presented by Mancy, Okun and Reilley (1962). The principle is demonstrated in figure 2, where a single polarizing pulse has been applied to the cathode of a polarographic electrode. The lower portion of this figure shows the electrode response. The leading edge of the pulse produces a capacitative charging of the electrical double layer at the cathode surface (shown as the initial spike), and the cathode current then decreases as oxygen is consumed, first

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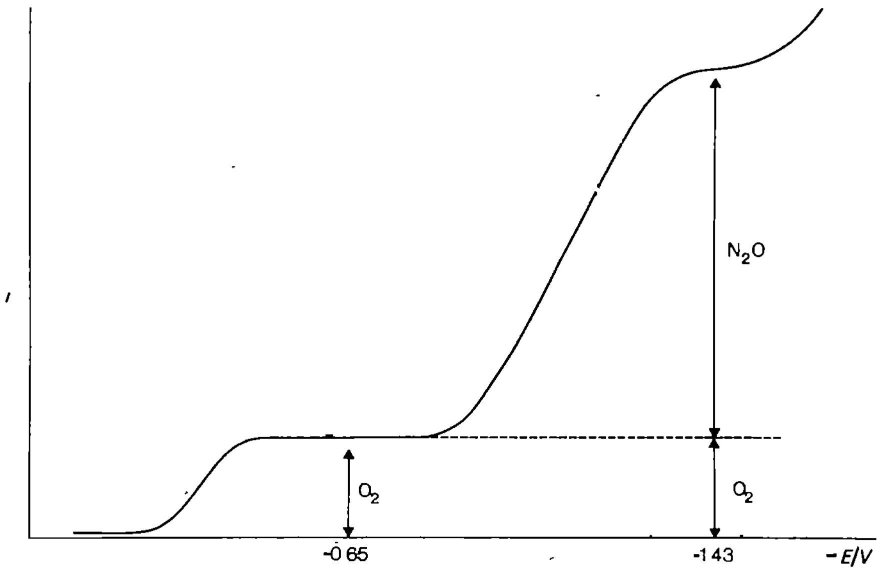

FIG. 1. A polarogram on a silver cathode, showing clear and distinct plateaux for the reduction of oxygen and nitrous oxide.

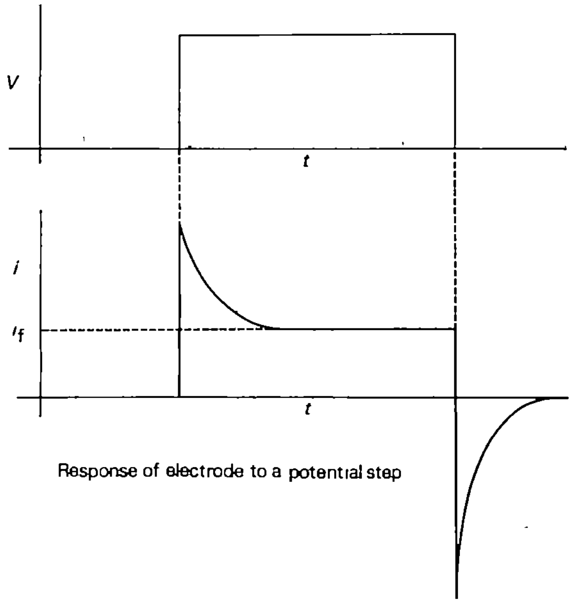

FIG. 2. The current response of an oxygen electrode when a step in potential is applied to the cathode. The initial spike at the onset of the pulse is a charging effect at the cathode surface; the remainder of the trace is a result of oxygen reduction. With a long pulse the current decays to its steady state value, i_f.

from the electrolyte layer and then from the plastic membrane. If the pulse is long enough (as in fig. 2) the usual steady-state polarization (steady output current) is produced. The trailing edge of the pulse then produces a discharge of the double layer, seen as a negative spike, and the electrode current returns towards its (zero) quiescent state. A second pulse for nitrous oxide merely repeats this pattern.

After the initial charging period, which lasts a few milliseconds, the electrode current is proportional to oxygen concentration at any given time after the beginning of the pulse (Hitchman, 1978). As seen in figure 2, when the steady state current is reached, the current no longer decreases with increasing time.

The electrodes used in the study reported below were of the neonatal type (G. D. Searle & Co. Ltd, Size 5FG) with an outside diameter of 1.7 mm.

An integrated circuit double-pulse generator, and a dual sample-and-hold unit, were used to apply the required pulse train to the *in vivo* electrode, and to observe the resultant oxygen and nitrous oxide currents.

The pulse durations were 2.88 s for oxygen reduction, and 3.15 s for nitrous oxide reduction. There was a 0.96-s pause between these two pulses, and the nitrous oxide pulse was followed by a 7.09-s pause. The oxygen and nitrous oxide currents were both sampled 0.1 s before the end of each pulse.

Mass spectrometer

The Centronic Medical Gas Analyser (200 MGA, T. C. Centronic Ltd), with a blood-gas stainless steel catheter attachment (Brantigan, Gott and Martz, 1972; Foëx et al., 1978) was used to provide a continuous record of arterial oxygen, carbon dioxide, nitrous oxide and halothane tensions. Previous work (Foëx et al., 1978, 1979) has shown that this instrument is linear with changes in blood-gas oxygen and carbon dioxide tension, and that $P\text{O}_2$ and $P\text{CO}_2$ readings obtained with it agree with conventional blood-gas analysis. The mass spectrometer was not used in its "ASC" (automatic sensitivity control) mode, since the sum of the partial pressures of all of the gases in the arterial blood was unknown. The instrument was calibrated *in vitro*, before insertion of the catheter to the artery, by placing the catheter tip in saline in an Adams tonometer (Adams and Morgan-Hughes, 1967) at 37 °C and tonometering the saline with an oxygen–nitrous oxide mixture (50% : 50%). The electrical output from the mass spectrometer was connected to a signal conditioning unit with a digital read out, and the oxygen (mass 32) and nitrous oxide (mass 30) channels were each scaled to read "50 kPa". Thereafter, the catheter was immediately inserted to the artery.

Animal model

Four dogs were studied. In each dog anaesthesia was induced with pentobarbitone 25 mg kg^{-1} and maintained by supplements of this agent. After endotracheal intubation intermittent positive pressure ventilation was maintained with an Oxford–Penlon ventilator set to deliver a total volume of 40 ml kg^{-1} at a rate of 12 b.p.m. $F\text{I}_{\text{CO}_2}$ was set at 0.04 and $F\text{I}_{\text{O}_2}$ 0.96. The catheter polarographic electrode and the mass spectrometer catheter were inserted to the abdominal aorta via the femoral arteries, and a blood sampling catheter was inserted to the aortic arch via the carotid artery. The dog was chosen as the experimental model because its femoral arteries are large enough to admit the catheters and its haemodynamic responses to anaesthesia are well documented.

Gas analysis and other measurements

Inspired oxygen, carbon dioxide and nitrous oxide were measured with carefully checked flowmeters and halothane was added from a Dräger vaporizer. The inspired halothane concentration was checked with a Hook and Tucker ultra violet halothane meter, and $F\text{I}_{\text{O}_2}$ with a paramagnetic analyser (Servomex OA272) (Nunn, 1964). Inspired and expired carbon dioxide were measured with an infra-red carbon dioxide analyser (Capnograph model URAS 4/2WO). The data from the mass spectrometer were recorded on a four-channel pen recorder (Devices M4-120). The current signals from the *in vivo* electrode were displayed on a Gould Advance OS4000/4001 digital storage oscilloscope, which allowed hard copies of the transient signals to be recorded periodically on a Bryans 29000 A3 *X/Y/t* recorder. Both the oxygen and nitrous oxide currents were displayed continuously on digital voltmeters.

PROCEDURE

The *in vivo* electrode was activated by immersion in saline at 37 °C in the Adams tonometer, and its linearity was checked by tonometering the saline with oxygen–nitrous oxide mixtures obtained from Wösthoff gas mixing pumps (Model M300/a-F).

After insertion of the mass spectrometer catheter and the *in vivo* electrode into the femoral arteries, the mass spectrometer $P\text{O}_2$, $P\text{CO}_2$ and $P\text{N}_2\text{O}$ values were continuously recorded on the chart recorder. These records were used to define when a steady blood-gas state was reached—usually within 10–12 min of changing the inspired gases.

After the initial steady-state had been reached, arterial blood was sampled for immediate gas analysis and a hard copy record of the *in vivo* electrode oxygen and nitrous oxide signals was obtained; the oxygen and nitrous oxide signals on the digital voltmeters were noted. Arterial $P\text{O}_2$, $P\text{CO}_2$ and pH were obtained from standard Radiometer electrodes, which had been carefully checked to ascertain that they were free from either nitrous oxide or halothane interference (Douglas et al., 1978; Evans and Cameron, 1978).

Nitrous oxide was then added to the inspired gas mixture in steps increasing by 10% v/v, and $F\text{I}_{\text{O}_2}$ was diminished accordingly. $F\text{I}_{\text{CO}_2}$ was adjusted, when necessary, so that the end-tidal carbon dioxide concentration was kept constant at 5.3% v/v. The ventilation was kept constant at all times.

Since only steady state, and not transient, changes were examined in this study, the mass spectrometer was used to define when new steady blood $P\text{O}_2$, $P\text{CO}_2$ and $P\text{N}_2\text{O}$ values had been obtained. Readings were then taken from the flowmeters, paramagnetic analyser, carbon dioxide analyser, and from the in-dwelling catheter systems.

Halothane was not introduced until the end of the nitrous oxide investigation. A 50% oxygen–4% carbon dioxide–46% nitrous oxide inspired gas

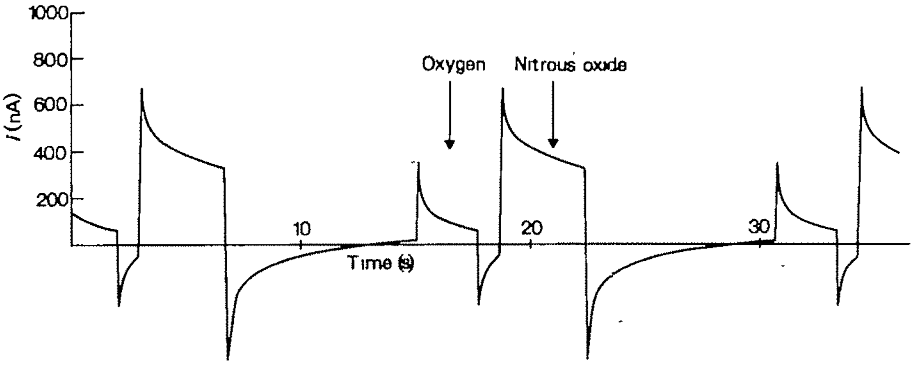

FIG. 3. A tracing of the intravascular electrode response to a train of polarizing pulses, showing the electrode current for the oxygen and nitrous oxide concentrations in the blood.

mixture was used as a control, and *in vivo* readings were obtained as indicated above. Halothane was then introduced, commencing at 0.5% v/v. When the mass spectrometer indicated that the blood halothane concentration was constant, the *in vivo* catheter signals were recorded. The halothane concentration was increased in two steps to 0.9% v/v and 1.2% v/v, and the data recorded as above.

Finally, the inspired gases were returned to their initial control values ($FI_{O_2} = 0.96$, $FI_{CO_2} = 0.04$), to check that the *in vivo* electrode had not drifted unduly during the 4 h duration of each experiment.

RESULTS

An example of the oxygen and nitrous oxide current signals obtained from one *in vivo* catheter electrode is shown in figure 3. During each of the four experiments, a good correlation was observed between the electrode oxygen current and measured Pa_{O_2} obtained by bench blood-gas analysis. Since the electrode output current varied between electrodes depending upon the membrane thickness and the exact diameter of each cathode, the slopes of the current-Po_2 relationship differed from experiment to experiment.

A comparison of 37 determinations on four electrodes in four dog studies is shown in figure 4. The electrode oxygen current has been normalized to the individual straight lines in each study, so that each electrode reading is displayed in (normalized) kPa units, rather than nanoamps. The line of identity is also drawn in figure 4, and it can be seen that the actual data points show a good fit to the line of identity, with a correlation coefficient of 0.99.

Since each dog study gave the same general response, the following results examine the details of

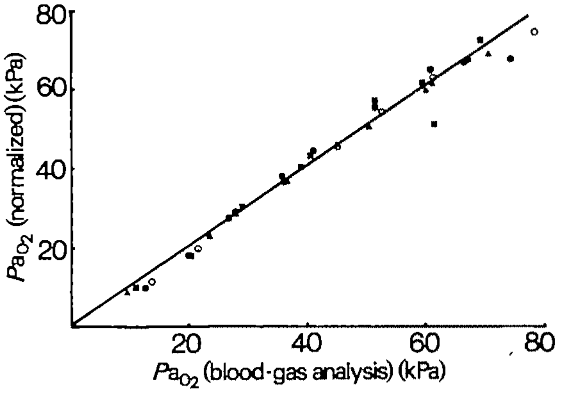

FIG. 4. A plot of normalized *in vivo* electrode oxygen readings against Po_2 values obtained from blood-gas analysis of discrete samples. Thirty-seven determinations from four dog studies are shown, together with the line of identity.

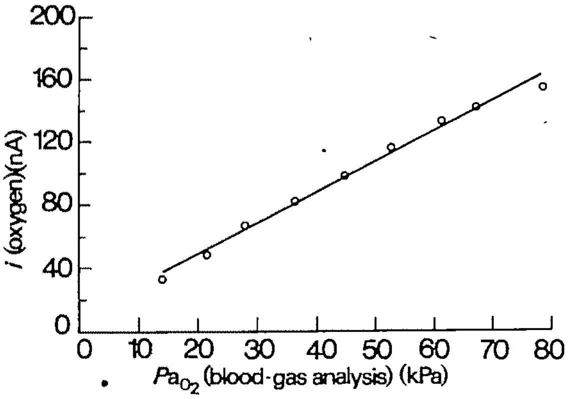

FIG. 5. A plot of the intravascular electrode oxygen current, against Po_2 values from discrete blood samples obtained at the same time and analysed in a blood-gas analyser.

the pulsed electrode oxygen and nitrous oxide response in one study.

Oxygen response

Figure 5 shows the relationship between the pulsed electrode current (displayed on the digital voltmeters) and the Pa_{O_2} (blood-gas analyser) of the simultaneously sampled arterial blood. A good correlation is shown.

Figure 6 shows the agreement between the simultaneous readings from the pulse catheter electrode and the mass spectrometer.

Nitrous oxide response

The agreement between the *in vivo* electrode nitrous oxide current and the inspired nitrous oxide gas concentration is shown in figure 7. The FI_{N_2O} values were calculated from the inspired oxygen and carbon dioxide values, obtained from the Servomex and carbon dioxide analyser. Similar results were obtained with FI_{N_2O} values obtained directly from the flowmeter settings.

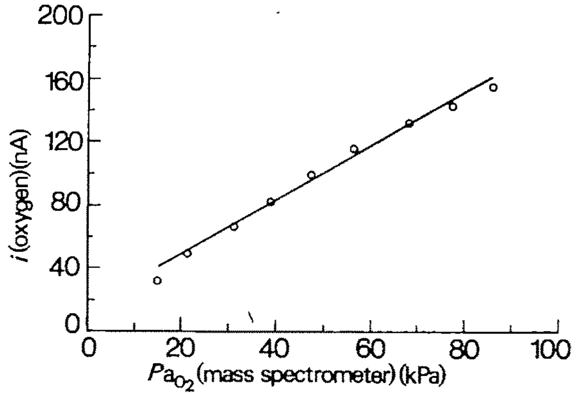

FIG. 6. A plot of the intravascular electrode oxygen current against the simultaneous P_{O_2} readings obtained with the mass spectrometer blood-gas catheter.

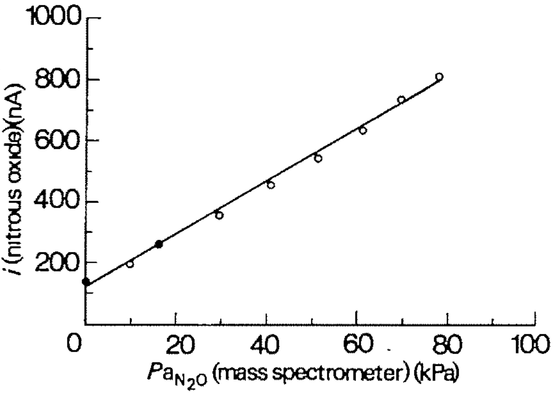

FIG. 8. A plot of the intravascular electrode nitrous oxide current against the simultaneous nitrous oxide readings obtained with the mass spectrometer blood-gas catheter.

Figure 8 shows a good correlation between the pulsed electrode nitrous oxide current and Pa_{N_2O}, measured with the mass spectrometer.

Halothane effect

When halothane was added progressively to an otherwise constant inspired gas mixture (50% oxygen–4% carbon dioxide–46% nitrous oxide), the oxygen current increased (fig. 9) as did that for nitrous oxide (fig. 10) although rather erratically.

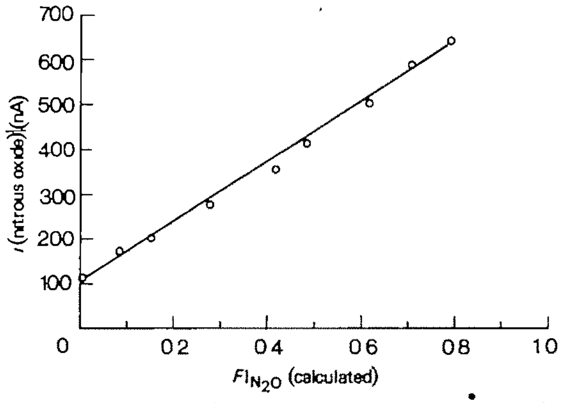

FIG. 7. A plot of the intravascular electrode nitrous oxide current against the inspired nitrous oxide gas concentration calculated from the oxygen and carbon dioxide gas analysers: $FI_{N_2O} = 1 - FI_{O_2} - FI_{CO_2}$.

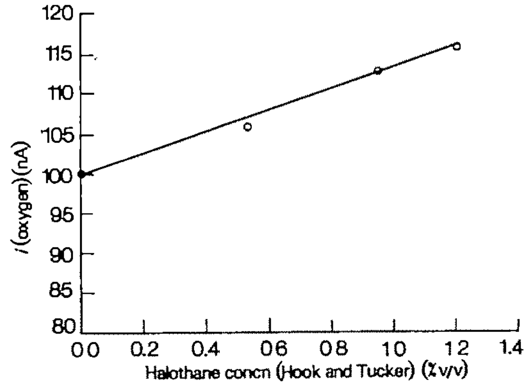

FIG. 9. The increase in the intravascular electrode oxygen current, when the inspired oxygen–nitrous oxide–carbon dioxide concentration was kept constant at 50 : 46 : 4, but halothane was added in increasing amounts to 1.2% v/v.

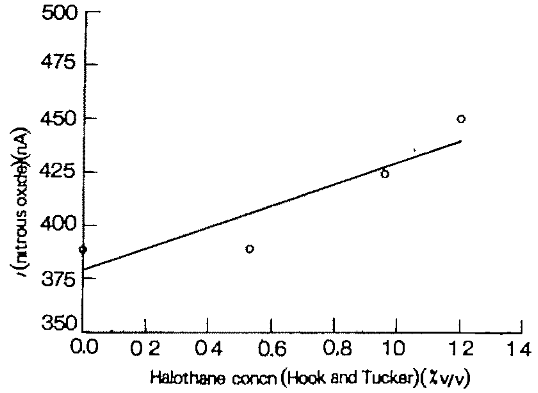

FIG. 10. The nitrous oxide response of the same electrode as in figure 9 when inspired halothane was increased in amounts up to 1.2% v/v. Apart from halothane, the inspired oxygen–nitrous oxide–carbon dioxide ratio was kept constant at 50 : 46 : 4.

The mass spectrometer showed that Pa_{O_2} and Pa_{N_2O} were essentially constant during this period and this was confirmed for Pa_{O_2} by measurements on isolated arterial samples. The changes illustrated in figures 9 and 10 were therefore an effect of halothane on the pulsed electrode.

This halothane effect was observed in the three other dog studies, although the exact magnitude depended upon the current sensitivity of each electrode.

DISCUSSION

Pulsing in vivo

The results have confirmed our impressions from studies *in vitro* (Hahn et al., 1979) that it might be possible to use a pulsed catheter electrode for quantitative *in vivo* Po_2 and PN_2O measurement. The electrodes have proved to be stable and linear when used in a pulsed mode. Other workers (for example, Lilley, Story and Raible, 1969; Schmid and Mancy, 1970) have applied this method to membrane-covered electrodes for the analysis of small concentrations of dissolved oxygen in waste water, but to the best of our knowledge our work is the first application of the pulse technique to *in vivo* catheter electrodes—especially for measuring two separate gas components with the same electrode. Other advantages of pulsing, such as very low oxygen consumption and the independence of the electrode on membrane permeability characteristics, are under investigation in our laboratories. With hindsight, we would not have employed such long time pulses in this study, as very short pulses would reduce the oxygen consumption of the electrode and therefore reduce the flow effect (Rolfe, 1976) for the electrode.

Oxygen and nitrous oxide analysis

Figures 5–8 show that both Po_2 and PN_2O can be measured simultaneously on the same catheter electrode *in vivo*. Evans and Cameron (1978) have quoted that nitrous oxide can seriously interfere with the measurement of Po_2 in arterial blood samples. However, our results have shown that the combination of the pulsing techniques with a silver cathode allows an investigator to measure either, or both, gas components in the blood phase. The electrode current was measured in absolute units (nanoamps) in this study, but the linearity of the results (figs 5, 6) indicates that it would be possible to scale the oxygen sensor output in kPa or mm Hg, as with standard neonatal oxygen probes.

Although figures 7 and 8 indicate that the nitrous oxide *in vivo* response of the electrode is also linear, it is not possible to calibrate the electrode by withdrawing a blood sample and analysing it with an *in vitro* analyser. Work is proceeding in our laboratories to solve this problem.

The solution to this problem may lie in applying very short pulse times to the electrode, since this should reduce the blood-gas, or stirring, factor to negligible proportions. An electrode could then be calibrated *in vitro*, in water-saturated gas at 37 °C, before insertion to an artery.

Pulsed intravascular electrodes will enable the anaesthetist to monitor Pa_{O_2} continuously, without fear of nitrous oxide interference, whether in the operating theatre or intensive therapy unit. The method will also permit the investigator to examine, in detail, the uptake of nitrous oxide by blood, in either animals or humans.

Halothane effects

Figures 9 and 10 confirm the findings of others that halothane greatly affects the performance of oxygen electrodes (Severinghaus et al., 1971; Bates, Feingold and Gold, 1975; Dent and Netter, 1976; Douglas et al., 1978; McHugh, Epstein and Longnecker, 1979), and that it often exaggerates grossly the Po_2 readings. The most recent study by McHugh, Epstein and Longnecker (1979) was confined to platinum and gold cathode electrodes, but the study by Bates, Feingold and Gold (1975) was directed particularly at silver cathode *in vivo* electrodes. Our own results have been confined to silver cathodes, but show that the electrode nitrous oxide signal is also affected by the presence of halothane in blood. The magnitude of this effect varied from dog to dog, and from electrode to electrode. The P_{O_2} signal was increased typically by about 15%, when the dog was ventilated with 1.2% halothane.

The conclusion is that it is impossible to measure arterial P_{O_2} accurately *in vivo* with a silver cathode electrode in the presence of halothane unless the electrode membrane material was impermeable to halothane. Commercial oxygen catheter electrode membranes are obviously permeable to halothane, and a change in membrane material is needed if these electrodes are to be used with halothane anaesthesia.

We are therefore puzzled by the results of Armstrong and colleagues (1976), since they used the Searle electrode to register arterial P_{O_2} during one-lung oxygen–nitrous oxide–halothane anaesthesia and polarized the electrode at −0.8 V. We would deduce from our results that there must not only have been a substantial halothane contribution, but also a significant contribution from the rising portion of the nitrous oxide wave, at this polarizing voltage (Albery et al., 1978; Hahn et al., 1979). Our recommendation is therefore that these electrodes should not be used in the presence of halothane anaesthesia, until a halothane-impermeable membrane material is developed for *in vivo* use.

Studies nearing completion in our laboratories have indicated that the halothane polarographic wave is inseparable from the oxygen wave on silver cathodes.

ACKNOWLEDGEMENT

We are grateful to the Medical Research Council for providing a Research Studentship for Mr W. N. Brooks.

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ANALYSE LINEAIRE DE LA Po_2 ET DE LA PN_2O A L'AIDE D'UNE ELECTRODE CATHETER *IN VIVO*

RESUME

On a mis au point une technique pour la détermination *in vivo* de la Po_2 et de la PN_2O à l'aide d'une électrode cathéter utilisant une polarographie à double impulsion. Cette méthode a été évaluée au cours d'études effectuées sur des chiens, où l'on a comparé les lectures données par l'électrode à celles émanant d'un spectromètre de masse utilisant une sonde *in vivo*. Les lectures concernant l'oxygène, obtenues à partir de l'électrode cathéter, ont aussi été comparées aux valeurs obtenues par l'analyse normale sang-gaz. On a observé une bonne corrélation entre l'électrode et le spectromètre de masse qu'il s'agisse de Po_2 ou de PN_2O. On a trouvé une corrélation similaire entre les lectures de l'électrode et l'analyse sang-gaz pour la Po_2. En présence d'halothane, les lectures de l'électrode ont été faussées pour la Po_2 et la PN_2O; et nous suggérons donc un remède à cela. L'électrode *in vivo* est un moyen efficace et moins onéreux que l'usage du spectromètre de masse pour la mesure linéaire de la Po_2 et de la PN_2O *in vivo*.

Po_2 UND PN_2O-ANALYSE MIT EINER *IN VIVO*-KATHETERELEKTRODE

ZUSAMMENFASSUNG

Eine Methode für *in vivo*-Bestimmung von Po_2 und PN_2O mit Katheterelektrode und Doppelpuls-Polarographie wurde entwickelt, und an Hunden versucht, wobei Ablesungen von der Elektrode mit denen eines Massenspektrometers mittels einer *in vivo*-Probe verglichen wurden. Die Sauerstoffablesungen von der Katheterelektrode wurden auch mit Werten einer konventionellen Blutgasanalyse verglichen. Gute Übereinstimmung wurde zwischen Elektrode, Spektrometer und Blutgasanalyse für Po_2 und PN_2O erzielt, während bei Halothan die Elektrode sowohl für Po_2 als auch für PN_2O zu hohe Werte angab; Abhilfe wird vorgeschlagen. Die *in vivo*-Elektrode ist eine wirksamere und billigere Alternative zum Spektrometer für die *in vivo*-Messung von Po_2 und PN_2O.

ANALISIS EN SERIE DE Po_2 Y DE PN_2O MEDIANTE UN ELECTRODO RECTIFICADOR *IN VIVO*

SUMARIO

Se desarrolló una técnica para la determinación *in vivo* de Po_2 y de PN_2O mediante un electrodo rectificador y haciendo uso de polarografía de doble pulso. El método se evaluó en estudios efectuados en perros, comparando las lecturas obtenidas del electrodo con las obtenidas mediante un espectrógrafo de masas que utiliza una sonda *in vivo*. Las lecturas de oxigeno que se obtuvieron del electrodo restificador se compararon también con los valores obtenidos mediante los análisis convencionales de la sangre, siguiendo métodos gaseosos. Se observó una buena concordancia entre los resultados del electrodo y del espectrógafo de masas, tanto para el Po_2 como para el PN_2O. Se encontró una concordancia similar entre las lecturas del electrodo y el análisis gaseoso de la sangre para el Po_2. Las lecturas mediante el electrodo fueron excesivas para el Po_2 y para el PN_2O cuando se tomaron en presencia de halotano; se sugiere un remedio. El electrodo *in vivo* provee una alternativa más efectiva y más barata que el espectrógrafo de masas en lo que respecta a las mediciones en serie de Po_2 y PN_2O *in vivo*.

Br. J. Anaesth. (1980), **52**, 723

COMPARISON OF THE NEUROMUSCULAR BLOCKING PROPERTIES OF ORG NC 45 AND PANCURONIUM IN THE RAT, CAT AND RHESUS MONKEY

N. N. Durant, M. C. Houwertjes and J. F. Crul

SUMMARY

The neuromuscular and cardiovascular activities of pancuronium were compared with those of its 16β monoquaternary congener, Org NC 45, in the anaesthetized rat, cat and rhesus monkey. In the rat Org NC 45 was 3.4 times less potent as a neuromuscular blocking agent than was pancuronium. In the cat, both drugs were found to be approximately equally eliminated by the liver, whereas renal elimination was observed only with pancuronium. In the rhesus monkey, Org NC 45 was about 1.5 times less potent than pancuronium as a neuromuscular blocking agent. At doses approximately eight times that producing 80% twitch block, the neuromuscular block produced by Org NC 45 was significantly shorter in duration and recovery than that produced by pancuronium. In addition, these high doses of Org NC 45 did not produce the tachycardia which is seen with pancuronium. Org NC 45 showed less tendency than pancuronium to produce cumulative effects on repeated administration in the monkey. Both Org NC 45 and pancuronium were antagonized by anti-cholinesterases and aminopyridines. It is suggested that the lack of tachycardia with Org NC 45 may be related to the low cardio-selective anti-muscarinic potency of Org NC 45 previously reported in the cat and, together with its low renal elimination and lack of cumulative effects, Org NC 45 may be a clinically useful non-depolarizing muscle relaxant free of cardiovascular side-effects.

Many non-depolarizing neuromuscular blocking agents in clinical use cause tachycardia in man (Kennedy and Kelman, 1970; Coleman et al., 1972; Stoelting, 1972). These agents are known to block cardiac muscarinic receptors in experimental animals (Saxena and Bonta, 1970, 1971; Hughes and Chapple, 1976; Lee-Son and Waud, 1978); in addition pancuronium can also cause sympathetically-mediated activity in animals (Nana, Cardan and Domokas, 1973; Ivankovitch et al., 1975; Domenech et al., 1976; Docherty and McGrath, 1977, 1978). Thus, the exact mechanism by which non-depolarizing neuromuscular blocking agents produce tachycardia in man is not clear. Durant and others (1979) demonstrated that Org NC 45 (fig. 1), a monoquaternary homologue of pancuronium which is similar in neuromuscular blocking potency to pancuronium, blocks the cardiac muscarinic receptors in the cat only at doses many times greater than those producing submaximal neuromuscular block.

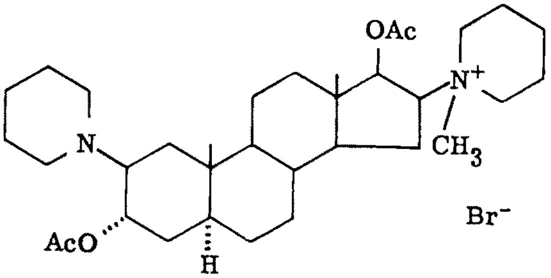

FIG. 1. Structural formula of Org NC 45.

We compared Org NC 45 and pancuronium in the rat, cat and rhesus monkey. Particular attention has been paid to the effect of Org NC 45 on the heart rate in the rhesus monkey and to the elimination of Org NC 45 in the cat, since both these factors are of clinical importance.

Some of this work was communicated at the Vth European Congress of Anesthesiology, Paris, September 1978 (Durant, 1978) and the American Society of Anesthetists meeting, San Francisco, October 1979 (Durant, Houwertjes and Agoston, 1979a, b).

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0007-0912/80/080723-08 $01.00

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METHODS

Anaesthetized rat sciatic nerve–tibialis anterior muscle preparation

Male rats (300–600 g) were anaesthetized with pentobarbitone sodium 60 mg kg^{-1} i.p. and the lungs were artificially ventilated with air at a rate of 100 b.p.m. and a tidal volume of 7 ml kg^{-1}. Body temperature was maintained at 37–38 °C and drugs were administered through a polythene cannula placed in a jugular vein. Arterial pressure was recorded via a polythene cannula placed in a carotid artery. The sciatic nerve was stimulated by rectangular pulses of 0.2 ms duration, a frequency of 0.1 Hz and at sufficient stimulus strength to elicit maximal twitch responses of the tibialis anterior muscle.

Anaesthetized cat sciatic nerve–tibialis anterior muscle preparation

Cats of either sex (2.4–4.5 kg) were anaesthetized with pentobarbitone sodium 40 mg kg^{-1} i.p. and were artificially ventilated with air at a rate of 26 b.p.m. and a tidal volume of 18 ml kg^{-1}. Body temperature was maintained at 36–38 °C and drugs were administered through a polythene cannula placed in a jugular vein. Arterial pressure was recorded via a polythene cannula placed in a carotid artery. The sciatic nerve in the popliteal space was stimulated with rectangular pulses of the same parameters as described above to elicit maximal twitch responses of the tibialis anterior muscle.

To exclude the liver from the general circulation, the method described by Agoston, Houwertjes and Salt (1980) was used.

Initially, a control dose of antagonist sufficient to produce an 80–90% reduction of twitch tension was administered via the jugular vein. The same dose was then used throughout the experiment. The second administration was made whilst the liver was by-passed for 10 min. The third administration was made via the portal vein. The fourth administration was a control given via the jugular vein, and the final administration was made whilst the liver was permanently by-passed. The sequence of the second and third administrations was reversed in half of the experiments.

To exclude the kidneys from the general circulation a clip was applied to the renal artery and vein of both kidneys.

Initially, a control dose of antagonist sufficient to produce an 80–90% reduction of twitch tension was administered via the jugular vein. The same dose was then used throughout the experiment. The second administration was made whilst the kidneys were temporarily excluded for 10 min. The third administration was a control, and the fourth and final administration was made whilst the kidneys were permanently excluded.

The time between administrations was 2 h for pancuronium and 1 h for Org NC 45; initial studies indicated that these two time intervals resulted in the minimum cumulative effect.

Anaesthetized rhesus monkey ulnar nerve–adductor pollicis muscle preparation

Rhesus monkeys of either sex (4.7–11.5 kg) were anaesthetized with ketamine hydrochloride 10 mg kg^{-1} i.m. and pentobarbitone sodium 30 mg total dose and were artificially ventilated with 67% nitrous oxide in oxygen at a rate of 20 b.p.m. and tidal volume of 12 ml kg^{-1}. Drugs were administered i.v. through an indwelling polyethylene cannula placed in the saphenous vein. E.c.g. was recorded (heart rate).

The ulnar nerve was stimulated via two polar subcutaneous needle electrodes with rectangular pulses of the same parameters as those described above. The twitch responses of the adductor pollicis muscle were recorded via a Statham UC3 transducer attached by a wire to a small U-clamp which could be fixed firmly to the basal phalanx of the thumb.

Drug and solutions

Drugs used were: 3,4-diaminopyridine, atropine sulphate, heparin, ketamine hydrochloride, neostigmine methylsulphate, pancuronium bromide, Org NC 45 bromide and pentobarbitone sodium. Org NC 45 was dissolved at a concentration of 1 mg ml^{-1} in 2.1 mg ml^{-1} of citric acid to prevent alkaline hydrolysis; a fresh solution was used for each experiment. Other drugs were dissolved in 0.9% saline. Doses are expressed as weight in terms of the salt when appropriate.

Statistics

Neuromuscular blockade during a drug effect was measured as the percentage depression of twitch tension relative to the height of the control twitch responses. Onset of neuromuscular blockade was measured as the time from injection to maximum depression of twitch tension, duration time as the time from injection to either 50% or 90% recovery of twitch height and recovery time as the time from 25% to 75% recovery of twitch height. Results are presented as the mean ± SEM of at least four observations except when indicated. The dose which produced a 50% inhibition of twitch tension was determined by regression analysis of the log-dose–effect curve. Comparisons of paired data were made with Wilcoxon's test and comparisons of unpaired data with the Mann–Whitney *U*-test. Probability values of less than 0.05 were regarded as significant.

RESULTS

Neuromuscular blockade

In the rat and rhesus monkey Org NC 45 was 3.4 and 1.5 times less potent respectively than pancuronium as a neuromuscular blocking agent (table I), but at submaximal blocking doses the time courses of the blocks produced by the two compounds were not significantly different (fig. 2, table II). At doses which produced submaximal neuromuscular block in the anaesthetized rhesus monkey there was no evidence of any change in heart rate with either pancuronium or Org NC 45 (fig. 3).

TABLE I. *Doses of pancuronium and Org NC 45 which produced a 50% reduction of twitch tension in the anaesthetized rat and rhesus monkey*

	Pancuronium (μg kg^{-1})	Org NC 45 (μg kg^{-1})
Rat tibialis anterior muscle	69.0	237.0
Monkey adductor pollicis muscle	5.4	8.1

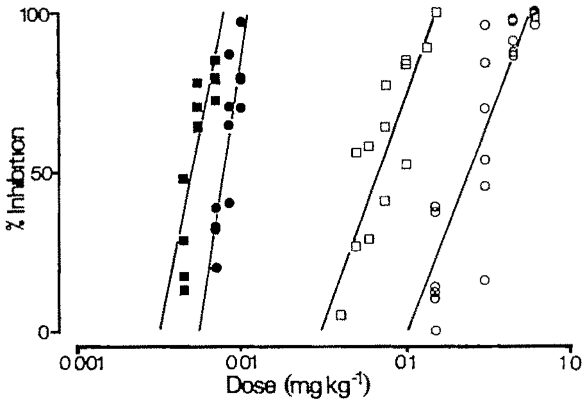

FIG. 2. Dose–inhibition plots for pancuronium (squares) and Org NC 45 (circles) on the rat tibialis anterior muscle preparation (open symbols) and monkey adductor pollicis muscle preparation (closed symbols).

Neuromuscular block produced by pancuronium and Org NC 45 was reversed in significantly faster time than control recovery by neostigmine 35 μg kg^{-1} and 3,4-diaminopyridine 1 mg kg^{-1} when injected at maximal block. At the doses used, 3,4-diaminopyridine caused marked bradycardia which was antagonized by a total dose of atropine 0.5 mg.

Cumulation studies

The cumulative effects of pancuronium and Org NC 45 were tested in the anaesthetized rhesus monkey by recording the depth and duration of neuromuscular block produced by six administrations of one of three different doses of either drug. Each

TABLE II. *Comparison of the time-course of neuromuscular block produced by pancuronium and Org NC 45 in anaesthetized rats, cats and monkeys* (n = 4 *minimum*). **Significantly different from pancuronium* (P < 0.05)

Preparation	Dose (μg kg^{-1})	% Block	Onset (min)	Duration to 50% (min)	Recovery time (min)	Heart rate (%Δ)
Pancuronium						
Rat tibialis	100	92 ± 2	2 ± 0.3	4 ± 0.4	1 ± 0.2	—
Cat tibialis	22	88 ± 5	7 ± 1	14 ± 2	5 ± 0.8	—
Monkey adductor pollicis	7	80 ± 3	7 ± 1	15 ± 3	9 ± 3	1 ± 6
Monkey adductor pollicis	55	100	3 ± 0.6	111 ± 7	81 ± 4	+6 ± 2
Org NC 45						
Rat tibialis	450	90 ± 3	2 ± 0.1	4 ± 1.0	1 ± 0.4	—
Cat tibialis	25–40	81 ± 6	5 ± 0.5	9 ± 1	5 ± 1.0	—
Monkey adductor pollicis	10	82 ± 4	8 ± 0.6	16 ± 2	7 ± 0.6	−2 ± 1
Monkey adductor pollicis	81	100	2 ± 0.1*	45 ± 4*	10 ± 2*	0

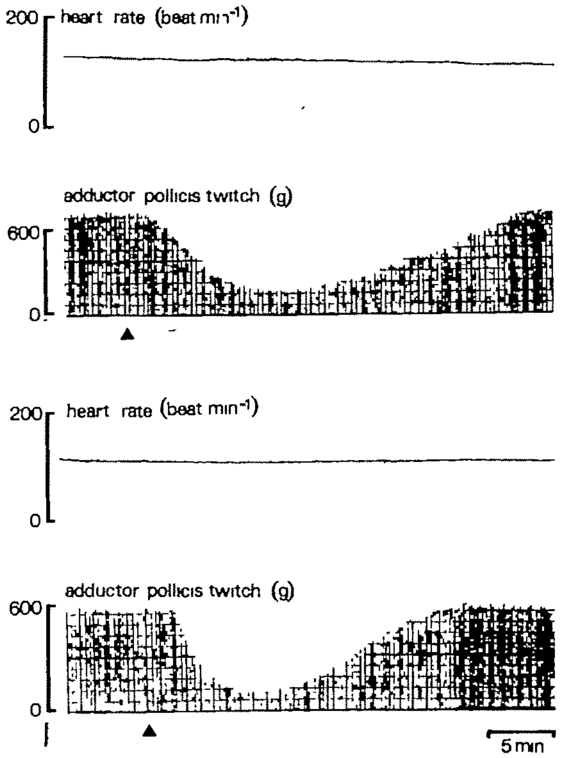

FIG. 3. Recordings from two typical experiments on the anaesthetized rhesus monkey showing the effects of pancuronium 7 μg kg⁻¹ (▲, upper tracings) and Org NC 45 10 μg kg⁻¹ (▲, lower tracings) on the twitches of adductor pollicis muscle and on the heart rate.

administration was made when recovery of twitch height from the previous administration had reached 90% of control height. Both pancuronium and Org NC 45 produced a greater depth of neuromuscular blockade with the second compared with the first administration (fig. 4). However, pancuronium exhibited a dose-dependent increase in duration of action up to the third administration, whereas Org NC 45 exhibited increase in duration only between the first and second administration (fig. 5). This suggests a slight difference between the pharmacokinetics of Org NC 45 and pancuronium in the rhesus monkey. Bolus administrations of the same multiple of equi-active neuromuscular blocking doses of pancuronium 55 μg kg⁻¹ resulted in a 6±2% increase in heart rate, but Org NC 45 81 μg kg⁻¹ was without effect. At these high doses, Org NC 45 was significantly more rapid in onset, shorter in duration and faster in recovery than pancuronium (table II).

Effect of exclusion of the liver

Temporary (10-min) exclusion of the liver in the cat resulted in a significant increase in the depth and duration of the neuromuscular block produced by both pancuronium and Org NC 45 compared with the first control doses of the drugs. Permanent exclusion of the liver also produced a significant increase in the depth and duration of the block produced by both drugs. Intra-portal vein administra-

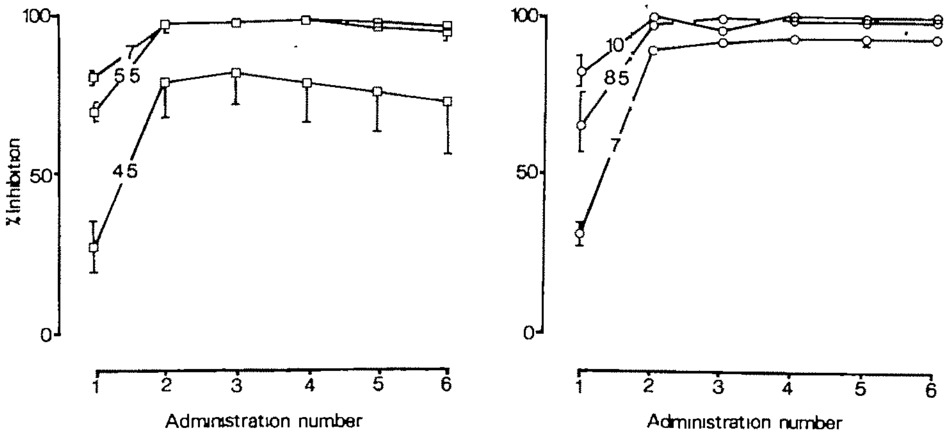

FIG. 4. The percentage depression of the twitch tension of the anaesthetized rhesus monkey ulnar nerve–adductor pollicis muscle preparation produced by six successive administrations of the three different doses of pancuronium (left, □) 4.5, 5.5 and 7.0 μg kg⁻¹, and Org NC 45 (right, ○) 7, 8.5 and 10 μg kg⁻¹.

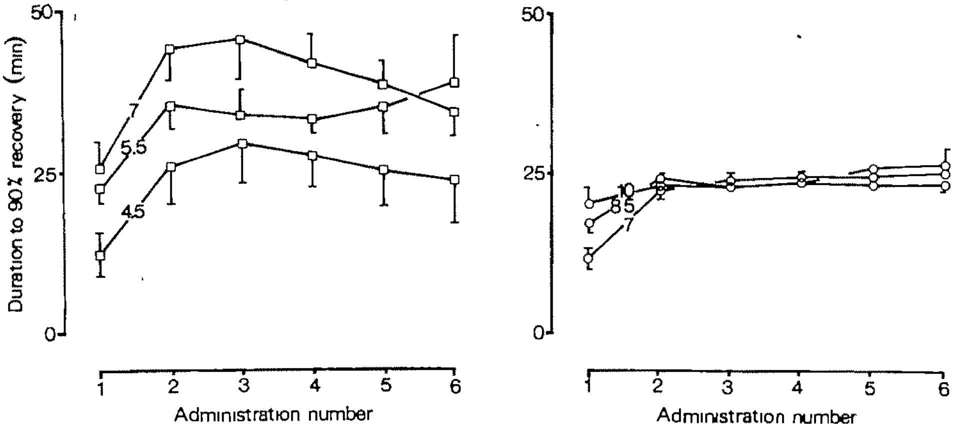

FIG. 5. The duration to 90% of recovery of twitch tension of the anaesthetized rhesus monkey ulnar nerve–adductor pollicis muscle produced by six successive administrations of three different doses of pancuronium (left, □) 4.5, 5.5 and 7.0 μg kg⁻¹, and Org NC 45 (right ○) 7, 8.5 and 10 μg kg⁻¹.

tion of Org NC 45 produced a neuromuscular block which was slightly smaller than control, but this did not occur with pancuronium (table III).

TABLE III. *Neuromuscular blockade of the sciatic nerve–tibialis anterior muscle preparation of the anaesthetized cat produced by pancuronium 22 μg kg⁻¹ and Org NC 45 25–40 μg kg⁻¹ with the liver temporarily and permanently excluded from the general circulation. The responses to intraportal vein (IPV) administration are also shown.* (n = 5; **significantly different from control*)

Drug and procedure	% Blockade	Onset time (min)	Duration to 50% (min)	Recovery time (min)
Pancuronium				
Control	92±7	6±2	15±4	5±1
10 min exclusion	100	3±1	26±2*	5±1
IPV	99±1	4±2	17±1	5±1
Control	98±2	4±1	17±2	4±1
Permanent exclusion	100*	2±0.2	No recovery at less than 45 min*	
Org NC 45				
Control	82±7	5±1	10±2	5±2
10 min exclusion	100*	3±0.3	19±1*	6±1
IPV	63±12	5±0.3	10±1	6±2
Control	98±1	4±1	12±1	6±1
Permanent exclusion	100*	2±1	28±9*	10±1*

Effect of exclusion of the kidneys

Temporary (10-min) exclusion of the kidneys did not have a significant effect on either the depth or duration of the neuromuscular block produced by either pancuronium or Org NC 45. Permanent kidney exclusion only significantly increased the duration (to 50% recovery) and decreased the onset time of the neuromuscular block produced by pancuronium, whereas the neuromuscular block produced by Org NC 45 was unaffected (table IV).

TABLE IV. *Neuromuscular blockade of the sciatic nerve–tibialis anterior muscle preparation of the anaesthetized cat produced by pancuronium 22 μg kg⁻¹ and Org NC 45 25–40 μg kg⁻¹ with both kidneys temporarily and permanently excluded from the general circulation.* (n = 5; **significantly different from control*)

Drug and procedure	% Blockade	Onset time (min)	Duration to 50% (min)	Recovery time (min)
Pancuronium				
Control	85±7	9±1	15±3	6±1
10 min exclusion	98±1	7±2	17±1	6±1
Control	96±2	6±1	17±3	6±1
Permanent exclusion	100*	3±1*	27±6*	8±2
Org NC 45				
Control	79±8	4±1	10±2	5±2
10 min exclusion	86±8	4±0.2	9±2	6±2
Control	78±11	4±1	10±2	5±1
Permanent exclusion	85±8	4±0.7	8±2	4±1

DISCUSSION

In all three species tested, Org NC 45 was slightly less potent than pancuronium as a neuromuscular blocking agent. At submaximal blocking doses both compounds had similar time-courses of action. The potencies of Org NC 45 and pancuronium in the cat in the present study are slightly greater than previously reported (Durant et al., 1979); this is most probably because of the different anaesthetics used. With large doses in the monkey the time-course of the neuromuscular block produced by Org NC 45 was shorter than that of pancuronium and the increase in heart rate associated with pancuronium was not seen. Org NC 45 has been demonstrated to have only a very weak blocking action at the cardiac vagus neuroeffector junction (Durant et al., 1979; Marshall and Ojewole, 1979) and no evidence has been found that Org NC 45 enhances noradrenergic transmission (Marshall and Ojewole, 1979). It is likely that this lack of autonomic effect at doses many times those blocking neuromuscular transmission explains the lack of cardiovascular side-effects reported by Booij and others (1980), and the absence of tachycardia in the present study.

The neuromuscular block produced by Org NC 45 was antagonized by anticholinesterases as easily as was the block produced by pancuronium, an essential requirement of any non-depolarizing muscle relaxant of potential clinical use. The neuromuscular blocks produced by both pancuronium and Org NC 45 were also antagonized by 3,4-diaminopyridine, a compound that is known to increase the evoked release of acetylcholine (Durant and Marshall, 1978). Based on neuromuscular block in the rhesus monkey, pancuronium and Org NC 45 exhibited similar cumulation characteristics in that both agents produced a greater depth of blockade with the second administration than with the first. This suggests, as previously demonstrated by Paton and Waud (1967) and Waud and Waud (1972), that considerable occupation of the receptors occurs when twitch responses have returned to control height after neuromuscular block. However, pancuronium produced a more pronounced increased duration of blockade with successive doses than did Org NC 45. This suggests that the pharmacokinetics of Org NC 45 are different from those of pancuronium in the rhesus monkey. The lower cumulative effects of Org NC 45 may be of some potential clinical benefit, as prediction of additional dosage should be straightforward.

Pancuronium is eliminated mainly by the kidneys in man (Agoston et al., 1973; Tanaka, Hioki and Shindo, 1974; Buzello, 1975) and has been shown to exhibit a prolonged action in patients with impaired renal function (Popescu, 1972; Miller, Stevens and Way, 1973; McLeod, Watson and Rawlins, 1976; Hull et al., 1978). Similarly, biliary obstruction can double the plasma half-life of pancuronium in man (Somogyi, Shanks and Triggs, 1977). The neuromuscular block produced by pancuronium administered via the intraportal vein was not significantly different from control in the present study, confirming that the liver uptake of pancuronium is small in the cat (Agoston et al., 1977). The biliary excretion of pancuronium, reported by Agoston and others (1977) and Miller and others (1978), was confirmed in the present study by the marked increase of the duration of the neuromuscular block when the liver was excluded.

The importance of the renal route of elimination of pancuronium in the cat is illustrated by the increase in the duration of neuromuscular blockade which accompanies renal occlusion of the circulation to the kidneys. However, neuromuscular blockade induced by Org NC 45 was not significantly altered by occlusion of the circulation to the kidneys. This observation may be explained in two different ways. First, the renal elimination of Org NC 45 is small; second, Org NC 45 is subject to rapid breakdown into non-active metabolites. In either case renal excretion of the intact molecule will be small.

The actions of Org NC 45 described, if observed in man, would make the drug a significant advance in the search for a more selective, shorter-acting muscle relaxant.

ACKNOWLEDGEMENTS

We acknowledge gratefully the help of Drs I. G. Marshall, S. Agoston and D. S. Savage with the organization of this project and preparation of the manuscript. We also wish to acknowledge the help of Dr C. Lee with the manuscript and Dr N. Krieg and Ms F. Van der Pol for assistance with some of the monkey experiments. One of us (N. N. D.) was the recipient of a Science Research Council C.A.S.E. award.

Pancuronium and Org NC 45 were supplied by Organon Scientific Development Group.

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COMPARAISON DES PROPRIETES DE BLOCAGE NEUROMUSCULAIRE D'ORG NC 45 ET DE CELLES DU PANCURONIUM CHEZ LE RAT, LE CHAT ET LE SINGE RHESUS

RESUME

On a comparé les activités neuromusculaires et cardiovasculaires du pancuronium à celles de son congénère monoquaternaire 16 β: Org NC 45, sur le rat, le chat et le singe rhésus anesthésiés. Org NC 45 a été 3,4 fois moins efficace sur le rat, en tant qu'agent de blocage neuromusculaire, que le pancuronium. Sur le chat, ces deux produits ont été trouvés à peu près équivalents du point de vue élimination par le foie, alors que leur élimination rénale n'a été observée qu'avec le pancuronium. En ce qui concerne le singe rhésus, Org NC 45 a été environ 1,5 fois moins efficace que le pancuronium en tant qu'agent de blocage neuromusculaire. A des doses à peu près huit fois supérieures à celles produisant un blocage à 80% de la

crispation, le blocage neuromusculaire produit par Org NC 45 a été nettement plus court du point de vue durée et récupération que celui occasionné par le pancuronium. De plus, ces fortes doses d'Org NC 45 n'ont pas produit la tachycardie que l'on constate avec le pancuronium. Org NC 45 a moins eu tendance que le pancuronium à produire des effets cumulatifs lors de l'administration répétée sur le singe. Org NC 45 tout comme le pancuronium ont été contrariés par les anticholinestérases et les aminopyridines. On pense que le fait qu'il n'y ait pas eu de tachycardie avec Org NC 45 peut être lié à la faible efficacité antimuscarinique cardio-sélective d'Org NC 45 que l'on avait précédemment constatée sur le chat, de même que par suite de sa faible élimination par voie rénale et de son manque d'effets cumulatifs. Org NC 45 peut être utile du point de vue clinique en tant que décontracturant musculaire non dépolarisant n'ayant aucun effet secondaire cardiovasculaire.

VERGLEICH DER NEUROMUSKULÄREN BLOCKIERUNGSEIGENSCHAFTEN VON ORG NC 45 UND PANCURONIUM BEI RATTEN, KATZEN UND RHESUSAFFEN

ZUSAMMENFASSUNG

Die neuromuskulären und kardiovaskulären Aktivitäten von Pancuronium wurden mit denen seines 16β monoquaternaren Stammesverwandten Org NC 45 in narkotisierten Ratten, Katzen und Rhesusaffen verglichen. Org NC 45 war, 3,4 mal schwacher als Pancuronium in der neuromuskularen Blockierungswirkung, wenn an Ratten verabreicht. Bei Katzen wurden beide Drogen etwa gleich gut von der Leber eliminiert, während es zu einer Eliminierung durch die Niere nur bei Pancuronium kam. Beim Rhesusaffen zeigte sich Org NC 45 etwa 1,5 mal schwächer als Pancuronium. Bei Dosen, die etwa achtmal grosser waren als die, die eine 80%ige Zuckblockierung bewirkte, war die von Org NC 45 bewirkte Blockierung von wesentlich kürzerer Dauer—bei kurzerer Erholungszeit—als mit Pancuronium. Ausserdem bewirkten diese hohen Dosen von Org NC 45 nicht wie Pancuronium eine Tachykardie. Org NC 45 zeigte auch geringere Tendenz als Pancuronium, bei wiederholter Verabreichung beim Affen kumulative Effekte zu bewirken. Beiden Drogen konnte durch Anticholinesterasen und Aminopyridine entgegengewirkt werden. Man nimmt an, dass die fehlende Tachykardie bei Org NC 45 auf die geringe kardio-selektive Anti-Muscarinstärke der Droge zurückzuführen ist, von der zuvor bei Katzen berichtet wurde; zusammen mit seiner niedrigen renalen Eliminierung und dem Fehlen kumulativer Effekte kann Org NC 45 als nicht-depolarisierendes Muskelentspannungsmittel ohne kardivaskulären Nebenwirkungen klinisch nützlich sein.

COMPARACION DE LAS PROPIEDADES DE BLOQUEO NEUROMUSCULAR DEL ORG NC 45 Y DEL PANCURONIUM EN LA RATA, GATO Y EN EL MONO RHESUS

SUMARIO

Se compararon las actividades neuromusculares y cardiovasculares del pancuronium con las de su congénere monocuaternario 163, el Org NC 45, en la rata, gato y en mono rhesus anestesiado. El Org NC 45 fue 3,4 veces menos potente en la rata, cual un agente de bloqueo neuromuscular, que el pancuronium. Se encontró que, en el caso del gato, el hígado eliminó ambas drogas por igual, aproximadamente, mientras que sólo se observó eliminación renal cuando se usó pancuronium. En el caso del mono rhesus, el Org NC 45 fue 1,5 veces menos potente, aproximadamente, que el pancuronium, a guisa de agente de bloqueo neuromuscular. Para dosis 8 veces superiores, aproximadamente, que las que producen un bloqueo de sustención del 80%, el bloqueo neuromuscular producido por el Org NC 45 fue significativamente mas corto en lo que respecta a su acción y recuperación, que el producido por el pancuronium. Además, estas altas dosis de Org NC 45 no produjeron la taquicardia característica del pancuronium. El Org NC 45 mostró menor tendencia que el pancuronium, a producir efectos acumulativos bajo administraciones sucesivas en el mono. Tanto el Org NC 45 como el pancuronium fueron contrarrestados mediante anticolinesterases y aminopiridinas. Se ha sugerido que la ausencia de taquicardia asociada con el Org NC 45 puede estar relacionada con la baja potencia cardioselectiva y antimuscarínica del Org NC 45, de la que se informó anteriormente para el gato y, junto con su baja eliminación renal y la ausencia de efectos acumulativos, el Org NC 45 puede que sea un relajante muscular no despolarizante de utilidad clínica que no presenta efectos secundarios cardiovasculares.

Br. J. Anaesth. (1980), **52**, 731

ANIMAL STUDIES OF THE ANAESTHETIC ACTIVITY OF ICI 35 868

J. B. GLEN

SUMMARY

The activity of a new i.v. anaesthetic agent ICI 35 868, a compound unrelated to currently used barbiturate, eugenol or steroid agents, has been examined in a range of animal species. Some of the properties of ICI 35 868 resemble those of thiopentone in that it is a rapidly acting agent which produces anaesthesia of short duration and without excitatory side-effects. Both agents have a similar therapeutic index and produce equivalent cardiovascular and respiratory effects. In the mouse ICI 35 868 is 1.8 times more potent than thiopentone as a hypnotic. However, the anaesthetic profile of ICI 35 868 differs from that of thiopentone in that recovery is rapid following repeated administration, no tissue damage is produced by perivascular or intra-arterial injection and greater reflex depression and more profound e.e.g. changes are produced at equipotent doses. This new agent has been shown to be compatible with a wide range of drugs used for preanaesthetic medication, inhalation anaesthetics, and neuromuscular blocking drugs.

Although sodium thiopentone is widely used for induction of anaesthesia, delay in recovery which is associated with repeated administration precludes its use for the maintenance of hypnosis during prolonged operations.

The more recently introduced i.v. anaesthetics are more rapidly metabolized, and hence more controllable, than thiopentone, but have failed to reproduce fully the quality of anaesthesia provided by thiopentone. I.v. anaesthesia utilizing an infusion of Althesin has been described by Savege and others (1975). This technique had the advantage of eliminating anaesthetic gases and vapours from the theatre environment, but did not always provide smooth easily-controlled anaesthesia, the principal complication found being movement.

Anaesthetic activity has been discovered in a series of hindered phenolic compounds which exist as oils at room temperature. These compounds can be administered i.v. in aqueous solution with the solubilizing agent Cremophor EL. Animal tests were designed to detect a compound which produced anaesthesia characterized by rapid onset, short duration, lack of cumulation on repeated administration, and a lack of excitatory effects on induction and during maintenance and recovery. Of the compounds examined only ICI 35 868 was found to have a desirable anaesthetic profile in animals.

The pharmacological effects of this compound are such that it is being developed as an agent suitable both for induction and maintenance of anaesthesia in man and animals. This paper describes the results of some experiments designed to evaluate the properties of ICI 35 868 in animals and to compare its activity with that of a range of currently used i.v. anaesthetics.

MATERIALS

The active agent in ICI 35 868 is 2,6-diisopropylphenol (fig. 1), a chemical entity unrelated to any of the currently used barbiturate, eugenol, or steroid anaesthetic agents.

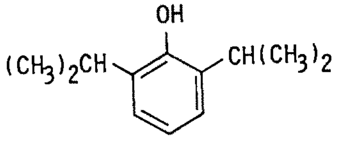

FIG. 1. ICI 35 868. 2,6-Diisopropylphenol.

The compound has low solubility in water at ambient temperatures, but aqueous solutions can be prepared using solubilizing agents such as Cremophor EL (polyoxyethylated castor oil, BASF) and other similar surfactants.

Single dose studies in rabbits and cats were carried out with ICI 35 868 administered as a 2% formulation in 10% Cremophor EL. In all the other studies suitable doses were prepared from a clinical trial formulation containing 2% ICI 35 868 in 16% Cremophor and 8.66% ethyl alcohol (all % w/v). In all species except mice the clinical trial

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0007-0912/80/080731-12 $01.00

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formulation was used in undiluted form. For experiments in mice the clinical trial formulation was diluted with distilled water to obtain preparations containing 1% and 0.5% ICI 35 868. In a later clinical trial formulation the active drug concentration was reduced to 1% and ethyl alcohol was omitted. No significant difference in anaesthetic activity has been produced in animals by the removal of ethyl alcohol from the formulation or by varying the amount of Cremophor EL in the formulation between 5% and 20%.

The mixture of anaesthetic steroids containing alphaxalone 9 mg and alphadolone acetate 3 mg per millilitre, which was used in some comparative studies, is described by the trade name Althesin (Glaxo) and doses refer to the total steroid content of the mixture, 12 mg ml^{-1} in the commercial preparation.

METHODS AND RESULTS

Anaesthetic activity: single dose studies

The anaesthetic activity of ICI 35 868 has been investigated in mice, rats, rabbits, cats, pigs and monkeys. Injections were made into the tail veins of mice and rats, the ear veins of rabbits and pigs, the cephalic vein in cats and the saphenous vein in monkeys. All injections were given over 10 s to mice and rats. In the larger species administration rates of 0.25–0.5 mg kg^{-1} s^{-1} were used.

Groups of 10 male Alderley Park mice (18–24 g body weight) were used at each dose tested. During the period of sleep mice were maintained at an ambient temperature of 35 °C. The dose required to abolish righting reflexes for a minimum period of 30 s in 50% of mice (the median hypnotic dose, HD$_{50}$) and the dose producing a lethal effect in 50% of mice (LD$_{50}$) were estimated by fitting parallel logit lines derived from the dose–response results.

The results obtained with ICI 35 868 and some other i.v. anaesthetics are given in table I. The activity of ICI 35 868 in mice was found to lie between that of thiopentone and methohexitone, being closer to the latter. No significant differences in the values for HD$_{50}$, LD$_{50}$ and therapeutic index were obtained when the activity of ICI 35 868 was examined in both male and female mice.

Using a technique described previously (Glen, 1977a) the speed of onset of effect of ICI 35 868 was compared with that obtained with some other anaesthetic agents. Values for HD$_{50}$ were determined using both a standard 10-s injection rate and a rapid (1-s) injection. Induction times were then noted

TABLE I. *Activity and lethality of ICI* 35 868 *and other i.v. anaesthetics in mice. (Figures in parentheses are* 95% *confidence limits)*

	HD$_{50}$ (mg kg^{-1})	LD$_{50}$ (mg kg^{-1})	Therapeutic index (LD$_{50}$/HD$_{50}$)
ICI 35 868	11.88 (10.86–12.98)	40.45 (36.79–44.47)	3.40 (2.99–3.88)
Thiopentone	21.68 (20.65–22.77)	84.69 (80.62–88.95)	3.91 (3.65–4.18)
Althesin	3.33 (3.13–3.55)	57.69 (53.94–61.70)	17.31 (15.79–18.98)
Methohexitone	7.93 (7.24–8.68)	37.66 (34.23–41.41)	4.75 (4.17–5.41)
Propanidid	21.19 (20.25–22.17)	118.0 (12.08–124.23)	5.57 (5.21–5.96)

TABLE II. *Induction times with ICI* 35 868 *and other i.v. anaesthetics in mice*

	1-s Injection		10-s Injection	
	HD$_{50}$ (mg kg^{-1})	Induction time(s) at 1.25 × HD$_{50}$	HD$_{50}$ (mg mg^{-1})	Induction time(s) at 1.25 × HD$_{50}$
ICI 35 868	7.5	4.8	12	10.7
Thiopentone	19.5	3.6	21.0	10.0
Althesin	2.5	3.6	3.3	12.4
Methohexitone	7.0	4.25	8.0	11.0
Propanidid	15.4	4.7	21.5	11.2

TABLE III. *The effects of ICI* 35 868 *and other i.v. anaesthetics in mice. Duration of sleeping time, recovery to walking, co-ordination, and respiratory rate (mean ± SD* (n= 10)). *Significant difference (Student's unpaired* t *test) from ICI* 35 868; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

I.v. anaesthetic	Sleeping time (min)	Interval between righting and walking (min)	Interval between righting and co-ordination (min)	Respiratory frequency (b.p.m.)
ICI 35 868 26 mg kg^{-1}	5.6 ± 1.3	1.3 ± 0.9	3.3 ± 1.1	169 ± 21
Thiopentone 40 mg kg^{-1}	9.9 ± 12.5	$0.6 \pm 0.4^{*}$	$47.8 \pm 6.5^{***}$	167 ± 22
Methohexitone 16 mg kg^{-1}	$2.0 \pm 0.5^{***}$	$0.5 \pm 0.2^{*}$	2.8 ± 0.6	186 ± 26
Althesin 7 mg kg^{-1}	$3.5 \pm 0.6^{***}$	0.8 ± 0.4	3.7 ± 0.9	$193 \pm 17^{**}$

following the injection of doses equal to 1.25 × HD$_{50}$, using both rates of injection.

The results obtained are given in table II. Induction times achieved with ICI 35 868 were similar to those found with other currently used rapidly-acting i.v. anaesthetic agents.

Additional experiments were performed in mice to investigate the effects on respiration, reflex depression, and recovery times achieved with ICI 35 868 and standard i.v. agents. ICI 35 868 26 mg kg^{-1} was given and effects compared with those of thiopentone, methohexitone, and Althesin at doses equivalent to 2 × HD$_{50}$ for these agents. Respiratory rates were counted with the aid of a low pressure transducer (Bradshaw, Biswas and Pleuvry, 1973) 1 min after induction of anaesthesia. Reflex depression was assessed with an artery clip applied to the tail and toes, and co-ordination was tested with a metal rod walking test. Mice were classed as co-ordinated when, on being placed on the rod, they either maintained their balance for 20 s or walked to the end of the rod within a shorter period. The duration of loss of righting reflex was noted and also the time required after righting before mice walked from the centre to the periphery of a 30-cm diameter disc.

TABLE IV. *The effect of ICI* 35 868 *and other i.v. anaesthetics on reflex depression in mice.* **Combined score for each group of* 10 *mice, the response being graded from* 0 (*no reflex response*) *to* 4 (*full reflex response*) *for each mouse.*

I.v. anaesthetic	Reflex depression* Time following injection (s) 10	20	30	60	120	180
ICI 35 868 26 mg kg^{-1}	0	0	4	22	38	40
Thiopentone 40 mg kg^{-1}	34	40				
Methohexitone 16 mg kg^{-1}	35	39	40			
Althesin 7 mg kg^{-1}	32	38	40			

The results given in tables III and IV show that mean sleeping time with ICI 35 868 was similar to that obtained with thiopentone and slightly longer than that found with Althesin and methohexitone. Recovery of walking ability returned after a similar period with all the drugs, but the slight difference between ICI 35 868 and the barbiturates was statistically significant. Following ICI 35 868, methohexitone and Althesin, mice regained co-ordination rapidly, whereas about 40 min elapsed before those mice given thiopentone had recovered completely. Respiratory rates obtained with thiopentone and ICI 35 868 were less than those found with methohexitone and Althesin, but only in the comparison with Althesin was this difference statistically significant.

A short period of 5–10 s of apnoea followed injection of ICI 35 868. This period of apnoea was not seen if a slower rate of injection was used. The degree of reflex depression associated with ICI 35 868 was greater than that seen with the other agents investigated. Recovery from the effects of ICI 35 868 and thiopentone was tranquil, whereas mice recovering from methohexitone and Althesin showed some muscle tremor and twitching, particularly when being handled in the co-ordination test.

Estimates of HD$_{50}$, LD$_{50}$ and therapeutic index were also made in rats using the technique already described for mice. Groups of 10 male rats (170–220 g) were used at each dose tested. In rats ICI 35 868 was

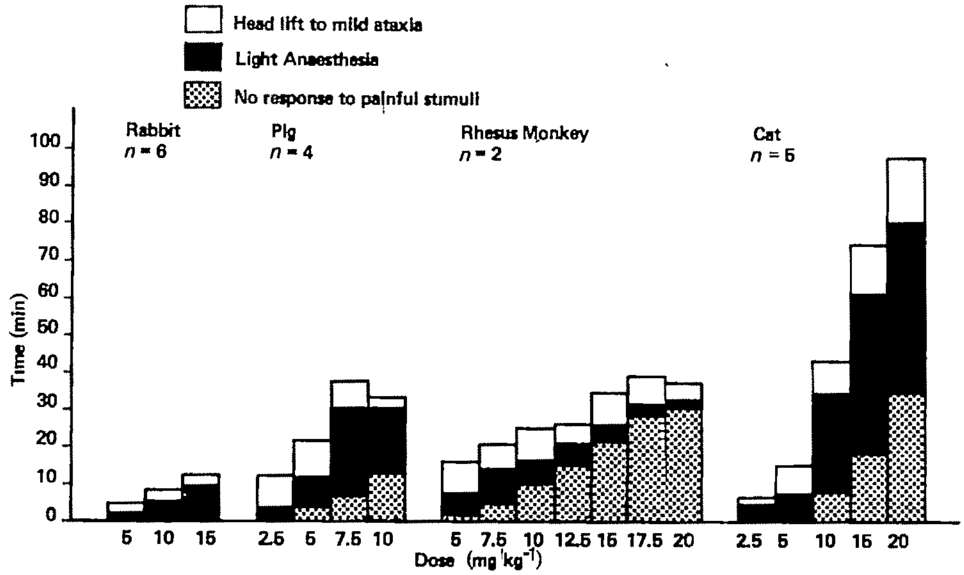

FIG. 2. Anaesthetic activity of ICI 35 868 in the rabbit, cat, pig and rhesus monkey.

TABLE V. *Dose–response effects of ICI* 35 868 *in the rat*

ICI 35 868 (mg kg^{-1})	Sleeping time (min) (mean ± SD)
5	3.03 ± 1.43
10	9.52 ± 1.63
25	17.37 ± 2.0
30	26.36 ± 6.28

found to have HD$_{50}$ 5.0 mg kg^{-1}, LD$_{50}$ 30.28 mg kg^{-1} and therapeutic index 6.06. Mean sleeping times with the doses used in this study are given in table V. With doses of 5 mg kg^{-1} and 10 mg kg^{-1} relaxation occurred 10–15 s after the end of injection, whereas greater doses induced anaesthesia immediately. With doses of 25 mg kg^{-1} and more, respiration was initially slow and shallow and cyanosis was noted. Muscle relaxation was good at all doses except the smallest where some tone persisted in rats which did not lose righting reflexes.

Dose–response effects produced by ICI 35 868 in the rabbit, cat, pig and monkey are shown in histogram form in figure 2. Anaesthesia was of very short duration in the rabbit and little reflex depression was obtained. In the other species, responses to painful stimuli were abolished with the larger doses used and the duration of anaesthesia increased. Induction and recovery were free from excitatory side-effects and good muscle relaxation was produced at all anaesthetic doses. A short period of apnoea occurred frequently in rabbits, cats and pigs following administration of the greater doses of ICI 35 868. In monkeys apnoea was seen only on one occasion, following a dose of 15 mg kg^{-1}. In two pigs the duration of apnoea following doses of 7.5 mg kg^{-1} was sufficient to warrant a short period of artificial ventilation. In these studies ICI 35 868 was administered on a total of 92 occasions. A lethal effect was obtained in six rabbits and one cat given a dose of 20 mg kg^{-1} when respiratory arrest occurred and no attempt was made to provide artificial ventilation. No sign of any delayed toxic effect was seen in the remaining animals which all recovered rapidly and were alert and keen to eat shortly after regaining the ability to walk.

Perivenous and intra-arterial administration

No vein damage occurred in any animal and no tissue necrosis followed the intentional perivascular injection of the 1% formulation of ICI 35 868 in 16% Cremophor EL in the mid-tail region of mice. This formulation also failed to produce any damage when given directly into the central ear artery in rabbits using the technique of Kinmonth and Shepherd (1959). In both of these circumstances thiopentone sodium 5% produced macroscopically obvious tissue necrosis.

I.m. administration

In rabbits ICI 35 868 60 mg kg^{-1} produced only moderate sedation after 12 min, suggesting that rapid metabolic breakdown or clearance of the agent in this species prevents the attainment of anaesthetic blood concentrations.

In one cat given ICI 35 868 20 mg kg^{-1} i.m., marked ataxia was produced after 12 min. A second cat given 36 mg kg^{-1} became increasingly sedated until righting reflexes were lost at 18 min after injection. Good relaxed anaesthesia then ensued for a further 1 h, but this large dose requirement was associated with a slow recovery.

E.e.g. effects

The e.e.g. effects of ICI 35 868 were investigated in 200-g male rats with previously implanted jugular venous cannulae and gold-plated cortical electrodes. Bipolar recordings were obtained from bilateral parietal electrodes. The e.e.g. changes produced by ICI 35 868 (fig. 3) were similar to those produced by rapidly acting barbiturates in this species. One difference noted was that burst suppression was produced at a dose close to the median hypnotic dose (HD_{50}), whereas the barbiturates only produced burst suppression when doses in excess of $2 \times HD_{50}$ were given.

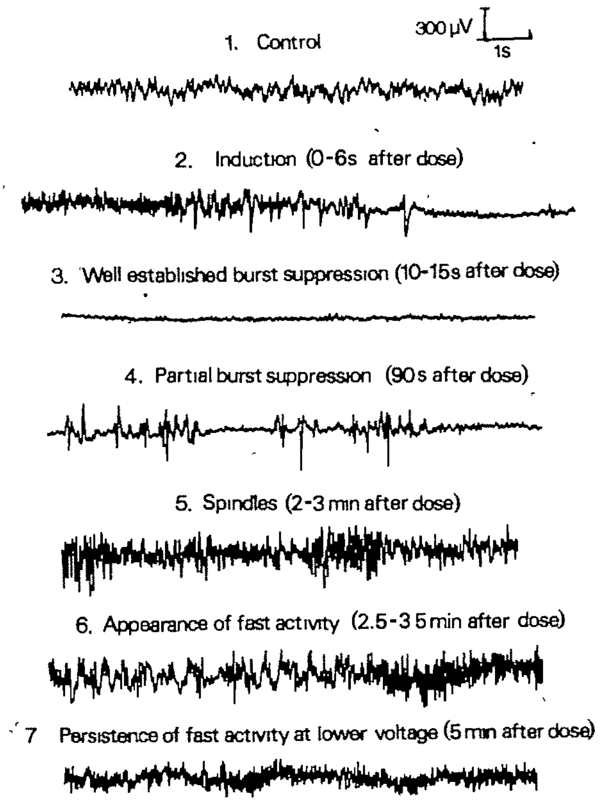

FIG. 3. E.e.g. effects of ICI 35 868 (8 mg kg^{-1} given over 12 s) in the rat.

Intermittent injection and infusion studies

Anaesthesia has been maintained by repeated injection or continuous infusion of ICI 35 868 in mice, rabbits, rats, cats and pigs. The rate of "utilization" of the compound in these species has been calculated by dividing the total dose administered by the duration of anaesthesia from induction to head-lift. Summary results are given in table VI. Species differences in the rate of utilization of ICI 35 868 are probably related to differences in the rate of bio-transformation and conjugation (C. Rhodes, personal communication), as the cat with the smallest "utilization rate" has a deficiency in its ability to conjugate phenols. Where the rate of administration of ICI 35 868 was just sufficient to maintain a light level of anaesthesia, head-lift occurred shortly after stopping an infusion and was little influenced by the duration of the maintenance period. With excessive rates of infusion some delay in recovery was noted.

TABLE VI. *Results obtained in intermittent injection and infusion studies*

Species	Mean "utilization rate" of ICI 35 868 (mg kg^{-1} min^{-1})
Mouse	2.22
Rabbit	1.55
Rat	0.61
Pig	0.28
Cat	0.19

Experiments were performed with mice to compare the cumulative effects of ICI 35 868 with those of

TABLE VII. *Sleeping times (min) with repeated doses of ICI 35 868, thiopentone and Althesin (mean ± SD;* n = 5). * n = 4; **n = 3; ***n = 2. *Remaining mice could not be given further injection because of mechanical damage to their tail veins*

Dose	ICI 35 868 25 mg kg^{-1}	Thiopentone 40 mg kg^{-1}	Althesin 12 mg kg^{-1}
1	4.6 (0.56)	3.86 (0.79)	6.03 (0.85)
2	7.1 (0.89)	30.3 (9.81)	8.6 (1.34)
3	8.4 (1.37)	148.6 (57.5)	9.5 (1.77)
4	10.0 (2.13)	> 180	13.7 (3.3)
5	10.8 (1.67)		10.4 (1.08)
6	10.2 (1.9)		18.2 (11.76)
7	10.8 (1.2)		16.2 (5.4)
8	11.7 (2.53)		17.6 (7.9)*
9	13.5 (2.9)		18.7**
10	15.4 (4.57)		18.3***

thiopentone and Althesin in this species. Groups of five mice were given doses of the test drug which produced a period of sleep of about 5 min. When righting reflexes returned 30 s was allowed to elapse before a further injection of the same dose was given. The sleeping time between successive injections was noted as an indication of the degree of cumulation occurring with each agent. The results given in table VII indicate that, in comparison with thiopentone, only slight cumulative effects were seen with ICI 35 868 and Althesin. With thiopentone, sleeping times were greater than 3 h after a fourth dose.

Haemodynamic and respiratory effects

Experiments were performed in Large White and Landrace pigs (17–40 kg) in which polythene arterial and venous cannulae had previously been implanted. The effects of ICI 35 868 were compared with those of equivalent doses of thiopentone and Althesin. All doses were given in a standard injection time of 30 s. Arterial pressure was measured with a strain-gauge transducer, heart rate was derived electronically from the arterial pressure record and arterial P_{O_2}, P_{CO_2} and pH were measured with standard Radiometer electrodes.

The effects on mean arterial pressure and heart rate are shown in tables VIII and IX. All three agents produced an initial hypotensive effect which was significant 1 min after injection. The hypotensive effect was accompanied by tachycardia which was most marked in animals given thiopentone and Althesin.

The results of blood-gas analyses are given in table X. All three agents investigated produced minimal changes in the variables measured.

Injection of Cremophor EL, in volumes equivalent to those used in the preparation of ICI 35 868 and Althesin, produced no detectable changes in arterial pressure or breathing.

The effect of ICI 35 868 and other i.v. agents on peripheral vasculature was investigated in two cats anaesthetized with chloralose 60 mg kg^{-1} i.v. Pressures were measured in a systemic artery and in an isolated perfused hind limb and acute effects of the anaesthetics on these variables were compared with those of the α-adrenergic blocking agent, phentolamine. In common with thiopentone and Althesin, ICI 35 868 produced dose-related reductions in pressure in an isolated perfused hind limb. This result indicates that at least a portion of the hypo-

TABLE VIII. *Effects of ICI 35 868, thiopentone and Althesin on mean arterial pressure (mm Hg) (mean ± SD; n = 7) in pigs. *Difference from pre-dose value significant at 1% level; **difference from pre-dose value significant at 0.2% level*

		Time after dose (min)					
	Before dose	1	2	3	4	5	20
Minimal induction doses							
Thiopentone 10 mg kg^{-1}	92	72**	98	101	98	97	94
	±12.0	±8.6	±15.0	±17.6	±15.3	±13.7	±17.8
% Δ		−21.7	+6.5	+9.8	+6.5	+5.4	+2.2
Althesin 1.8 mg kg^{-1}	91	78**	95	93	93	95	95
	±4.1	±8.5	±10.1	±8.3	±9.3	±10.2	±5.2
% Δ		−14.3	+4.4	+2.2	+2.2	+4.4	+4.4
ICI 35 868 2.5 mg kg^{-1}	90	71**	92	91	85	84	86
	±5.9	±10.9	±24.7	±23.1	±8.9	±8.1	±10.3
% Δ		−21.1	+2.2	+1.1	−5.6	−6.7	−4.4
Two × minimal induction doses							
Thiopentone 20 mg kg^{-1}	91	63**	101	109*	105**	104	99
	±2.7	±13.5	±9.6	±13.9	±9.7	±10.6	±5.4
% Δ		−30.8	+10.9	+19.8	+15.4	+14.3	+8.8
Althesin 3.6 mg kg^{-1}	91	75*	100	102	99	94	89
	±6.2	±9.3	±24.6	±12.8	±12.4	±6.9	±4.2
% Δ		−17.6	+9.9	+12.1	+8.8	+3.3	−2.2
ICI 35 868 5 mg kg^{-1}	91	64**	77	88	90	90	88
	±5.9	±10.5	±10.8	±7.8	±5.4	±4.7	±9.0
% Δ		−29.7	−15.4	−3.3	−1.1	−1.1	−3.3

tensive effect of these agents is the result of a decrease in peripheral vascular resistance.

Effect on bronchomotor tone

Airway pressure was monitored in three pigs during constant volume positive pressure ventilation with a Palmer pump. Pigs weighing 24–28 kg were anaesthetized with pentobarbitone and the trachea was intubated with a cuffed tube. ICI 35 868 0.5–4.0 mg kg^{-1} produced no effect on airway pressure. Subsequent administration of histamine 1–4 μg kg^{-1} produced detectable increases in airway pressure, an

TABLE IX. *Effects of ICI* 35 868, *thiopentone and Althesin on heart rate* (*beat* min^{-1}) (*mean* ± *SD*; n = 7) *in pigs*. **Difference from pre-dose value significant at* 1% *level*; ***Difference from pre-dose value significant at* 0.2% *level*

	Before dose	Time after dose (min) 1	2	3	4	5	20
Minimal induction doses							
Thiopentone 10 mg kg^{-1}	117	185**	149	152	150	147	124
	±21.7	±13.3	±27.0	±28.5	±31.3	±28.5	±28.5
% Δ		+58.1	+27.4	+29.9	+28.2	+25.6	+5.9
Althesin 1.8 mg kg^{-1}	137	191**	200**	201**	203**	199**	155
	±16.4	±27.2	±24.0	±23.9	±26.6	±25.4	±19.4
% Δ		+39.4	+45.9	+46.7	+48.2	+45.3	+13.1
ICI 35 868 2.5 mg kg^{-1}	112	153**	153**	149*	143	133	113
	±19.1	±16.5	±25.5	±23.8	±24.2	±18.9	±18.5
% Δ		+36.6	+36.6	+33.0	+27.7	+18.8	+0.9
Two × minimal induction doses							
Thiopentone 20 mg kg^{-1}	124	179**	180**	175**	171*	169	144
	±20.6	±15.6	±22.1	±29.4	±28.9	±30.1	±26.8
% Δ		+44.4	+45.2	+41.1	+37.9	+36.3	+16.1
Althesin 3.6 mg kg^{-1}	105	170**	173**	173**	171**	162**	133
	±27.0	±27.3	±37.1	±32.9	±22.4	±15.3	±22.7
% Δ		+61.9	+64.9	+64.8	+62.9	+54.3	+26.7
ICI 35 868 5 mg kg^{-1}	116	177**	171**	169**	161**	150	119
	±19.5	±25.0	±25.7	±28.5	±25.9	±24.1	±17.1
% Δ		+52.6	+47.4	+45.7	+38.8	+29.3	+2.6

TABLE X. *Arterial blood-gas values* (*mean* ± *SD*; n = 7) *in pigs anaesthetized with ICI* 35 868, *thiopentone and Althesin*. **Difference from pre-dose value significant at* 5% *level*; ***Difference from pre-dose value significant at* 1% *level*

	Before dose			3 min after dose			20 min after dose		
	pH	Po_2 (kPa)	Pco_2 (kPa)	pH	Po_2 (kPa)	Pco_2 (kPa)	pH	Po_2 (kPa)	Pco_2 (kPa)
Minimal induction doses									
Thiopentone	7.45	11.4	4.62	7.41	10.37	5.13	7.44	11.3	4.59
10 mg kg^{-1}	±0.02	±0.58	±0.38	±0.04	±1.95	±0.54	±0.02	±1.34	±0.58
Althesin	7.42	11.1	4.35	7.40	10.95	4.40	7.41	10.4	4.30
1.8 mg kg^{-1}	±0.03	±1.82	±0.55	±0.03	±1.53	±0.27	±0.04	±1.44	±0.38
ICI 35 868	7.44	11.3	4.36	7.39	10.6	4.58	7.42	11.0	4.44
2.5 mg kg^{-1}	±0.03	±1.69	±0.51	±0.04	±1.57	±0.70	±0.05	±1.50	±0.52
Two × minimal induction doses									
Thiopentone	7.42	11.5	4.34	7.39	9.68	5.37	7.43	10.9	4.69
20 mg kg^{-1}	±0.06	±1.05	±0.33	±0.05	±1.27*	±0.66**	±0.03	±1.13	±0.52
Althesin	7.46	11.3	4.43	7.40	9.43	4.89	7.44	10.4	4.60
3.6 mg kg^{-1}	±0.02	±1.43	±0.56	±0.03**	±1.25*	±0.91	±0.02	±1.11	±0.65
ICI 35 868	7.44	11.7	4.89	7.34	10.0	5.31	7.43	10.9	4.52
5 mg kg^{-1}	±0.04	±1.06	±0.60	±0.06**	±1.56	±0.61	±0.03	±1.03	±0.82

increase of 1.5 cm H_2O being obtained with the greatest dose of histamine given.

Cardiovascular reactivity

Cardiovascular responses to adrenaline, noradrenaline and acetylcholine were measured in conscious pigs and during anaesthesia maintained with an infusion of ICI 35 868.

The pressor response and reflex bradycardia obtained with both adrenaline and noradrenaline was greater in anaesthetized pigs, whereas the responses to acetylcholine were quantitatively very similar in both conditions. The increased pressor responses obtained with adrenaline and noradrenaline are partly explained by smaller pre-dose values in the anaesthetized state as the maximum values reached were similar in conscious and anaesthetized animals. No ventricular arrythmia was produced by the administration of adrenaline.

Effects of overdosage

Two experiments were conducted in cats to investigate the haemodynamic and respiratory effects of progressively increasing doses of ICI 35 868. Cats were allowed to recover to a light level of anaesthesia before a further dose of anaesthetic was given. In one cat artificial ventilation of the lungs was provided to counter the respiratory effects of large doses of ICI 35 868.

Anaesthesia was induced with ICI 35 868 10 mg kg^{-1} and preparations made to record arterial pressure, central venous pressure, Lead II electrocardiogram, heart rate and respiratory rate. The return of swallowing reflexes was the sign taken for the administration of a further dose of anaesthetic. For the first 1 h anaesthesia was maintained with minimal supplementary doses of ICI 35 868. This dose was found to be 2.5 mg kg^{-1}, administered at about 10-min intervals. The doses given subsequent to this period were gradually increased until a lethal effect was obtained.

No significant change in any of the indices was produced with doses less than 10 mg kg^{-1}. With doses of 10 mg kg^{-1} or more there was a period of apnoea and dose-related hypotension. When artificial ventilation was not used, the initial hypotensive effect was followed by a marked pressor effect, during the apnoea produced by doses of 15 mg kg^{-1} and 20 mg kg^{-1}. When spontaneous ventilation returned arterial pressure decreased again and then gradually returned to the pre-dose value over a period of 10 min. Heart rate decreased and central venous pressure increased during the initial hypotensive phase, indicating a negative inotropic effect of the drug at these large doses. In the cat where apnoea was prevented by artificial ventilation, large doses produced a hypotensive effect without any subsequent hypertensive response.

These experiments demonstrated that large doses of ICI 35 868 produce both respiratory and cardiovascular depression. With a dose of 20 mg kg^{-1} these effects combined to produce a lethal outcome when ventilation was not supported. With controlled ventilation one cat survived a dose of 30 mg kg^{-1} despite severe hypotension for a period. In this cat the degree of hypotension did not increase with increasing doses greater than 20 mg kg^{-1}.

Local anaesthetic effects

No surface anaesthesia was produced by the application of a 2% solution of ICI 35 868 to the rabbit cornea using the technique of Bulbring and Wajda (1945).

Interactions with drugs used in pre-anaesthetic medication

A selection of ataractic, sedative, anticholinergic and analgesic drugs was administered s.c. to mice 30 min before induction of anaesthesia with an i.v. injection of ICI 35 868 25 mg kg^{-1}.

The drugs and doses given were: droperidol 0.25 mg kg^{-1}; chlorpromazine hydrochloride 1.0 mg kg^{-1}; promethazine hydrochloride 2.5 mg kg^{-1}; diazepam 2.0 mg kg^{-1}; atropine sulphate 1.0 mg kg^{-1}; hyoscine hydrobromide 1.0 mg kg^{-1}; pethidine hydrochloride 1.0 mg kg^{-1}; papaveretum 2.5 mg kg^{-1}; pentazocine hydrochloride 10.0 mg kg^{-1}; pentobarbitone sodium 10.0 mg kg^{-1}; quinalbarbitone sodium 10.0 mg kg^{-1}; amylobarbitone sodium 10.0 mg kg^{-1} and 40 mg kg^{-1}.

A significant increase in sleeping time occurred following premedication with chlorpromazine, diazepam, papaveretum and the greater dose of amylobarbitone. A number of drugs including diazepam and droperidol caused delay in the recovery of walking ability and co-ordination, and a short but statistically significant delay in recovery was noted following atropine or hyoscine pre-medication. Pentazocine and amylobarbitone 40 mg kg^{-1} caused a significant slowing of respiratory frequency and papaveretum increased the duration of apnoea seen at induction. Following premedication with atropine and hyoscine there was no apnoea.

Further experiments showed that the magnitude of the potentiating effects of the preanaesthetic drugs on the action of ICI 35 868 was similar to that seen with Althesin. The combination of diazepam, droperidol or chlorpromazine with thiopentone produced much greater increases in sleeping times. The results of these experiments will be reported in more detail elsewhere.

Interactions with inhalation anaesthetics

Three adult cats (1.8–2.3 kg) were anaesthetized with each combination examined. Each cat was given an induction dose of ICI 35 868 7.5 mg kg^{-1} and the trachea was intubated following the application, in aerosol form, of lignocaine 10 mg to the laryngeal mucosa. The inspired concentration of each inhalation agent investigated was adjusted to maintain a light level of anaesthesia, the lower concentrations used being those required for maintenance of anaesthesia in this species. All agents, with the exception of cyclopropane were delivered to the cats via an Ayre's T-piece with fresh gas flows ranging from 1.5 to 4 litre min^{-1}. Cyclopropane mixtures, prepared in nylon reservoir bags, were administered through a unidirectional valve.

A summary of the main findings with each agent is given in table XI. Anaesthesia was maintained satisfactorily with all the inhalation agents tested and no unexpected interactions were observed. The responses of the cats during maintenance reflected the pharmacological properties of the inhalation agents employed.

Interactions with neuromuscular blocking drugs

Adult cats were used to investigate any possible interactions between ICI 35 868 and suxamethonium, gallamine and pancuronium. Pre-anaesthetic medication was restricted to atropine sulphate 0.2 mg administered i.m. 30 min before an induction dose of ICI 35 868 7.5 mg kg^{-1}. Anaesthesia was maintained with 0.5–2% halothane delivered via an Ayre's T-piece system. On a number of occasions the neuromuscular blocking drugs were antagonized with neostigmine and in some animals the non-depolarizing drugs were administered when recovery of spontaneous respiration had occurred following the administration of suxamethonium.

A summary of the experimental details and resluts is given in table XII. All the animals used in these experiments recovered uneventfully and no unexpected interactions were observed which could be related to the combination of ICI 35 868 with any of the neuromuscular blocking drugs investigated. Limb movements noted in one cat at the time of injection of pancuronium were attributed to the fact that the level of anaesthesia at that time was insufficient to prevent spontaneous movement when the animal was disturbed in the process of giving the injection.

TABLE XI. *Combination of ICI* 35 868 *with inhalation in cats. Figures are means from each group of three cats.* **Premedicated with atropine sulphate* 0.2 *mg* 30 *min before induction of anaesthesia*

			ICI 35 868 alone		Variables measured at the end of 1-h maintenance period			Recovery (min)	
Inhalation agent	Vol %	Carrier gases	Heart rate (beat min^{-1})	Resp. rate (b.p.m.)	Heart rate (beat min^{-1})	Resp. rate (b.p.m.)	Other observations	Head-lift	Walking
Halothane	0.5–2.0	O_2/N_2O 50/50	165	43	125	58	Uneventful maintenance period	9	11
Trichloroethylene	1.25–1.9	O_2	175	40	159	97	Multifocal ventricular extrasystoles in all three cats	25	36
Cyclopropane	20–30	O_2	168	37	115	27	Uneventful light level of anaesthesia	3	4.5
Enflurane	1.7–3.8	O_2	149	41	127	25	Uneventful light anaesthesia with 1.7%	5	7
Methoxyflurane	0.6–1.5	O_2	183	41	147	29	Uneventful maintenance period	19	24
Diethyl ether*	5.0–10	O_2	197	43	205	65	Uneventful maintenance period	12	31
Chloroform	1.25–2.0	O_2	165	38	139	95	Ventricular extrasystoles in two cats. Bradycardia in one cat	10	27

TABLE XII. *Combination of ICI* 35 868 *with neuromuscular blocking agents in cats.* **Residual relaxation antagonized with atropine* 0.2 *mg, neostigmine methyl sulphate* 0.1 *mg.* ***Relevant figures given as mean* ± *SD*

Neuromuscular blocking agent	Dose (mg kg^{-1})	No. of cats	IPPV required (min)	Duration of maintenance anaesthesia (min)	Recovery times (min)		Comments
					Head-lift	Walking	
Suxamethonium chloride	0.5	1	4	30	15	16	Transient bradycardia in one cat given 1.0mg kg^{-1}
	1.0	2	7, 19	30	19	23	
Pancuronium	0.06	1	24	30	5	8	
	0.08*	1	54	56	8	10	
Gallamine triethiodide	1.0	1	6	30	17	18	
	1.5	1	12	30	8	15	
Suxamethonium chloride + pancuronium**	0.5	4	5.1 ± 0.82	61 ± 5.31	9.8 ± 5.6	16 ± 6.8	Movement at time of injection of panc. in one cat
	0.06		36 ± 3.4				
Suxamethonium chloride + pancuronium**	0.5	3	8.5 ± 7.4	52 ± 2.88	7.7 ± 2.3	10.7 ± 1.2	
	0.06*		27.3 ± 1.5				
Suxamethonium chloride + gallamine	0.5	1	2.5	50	10	12	
	1.0*		21				

Because of the histamine-releasing properties of tubocurarine in the cat, the effects of this relaxant were investigated in pigs (12–22 kg) anaesthetized with an induction dose of ICI 35 868 5 mg kg^{-1} following premedication with atropine sulphate 0.3 mg and droperidol 2.5 mg. A Magill circuit was used during maintenance with 0.5–2% halothane in a total fresh gas flow of 6 litre min^{-1} of a 50 : 50 mixture of nitrous oxide and oxygen. Cuffed endotracheal tubes were used in pigs, suxamethonium being used to provide suitable conditions for intubation. Tubocurarine 0.15 mg kg^{-1} was given when spontaneous respiration had returned and a stable depth of anaesthesia achieved. Residual relaxation was readily reversed with neostigmine 1.25 mg in two pigs. All the pigs used in this study recovered uneventfully and no unexpected interactions were encountered.

In mice the combination of suxamethonium and propanidid causes a marked reduction in respiratory frequency, measured 2 min after injection of the mixture. The sleeping time produced by propanidid is also considerably extended (Glen, 1977b). The combination of ICI 35 868 with suxamethonium did not cause effects similar to those seen with the propanidid combination.

DISCUSSION

In a range of animal species the anaesthetic properties of ICI 35 868 have been found to be similar to those of thiopentone. Single doses of both agents produced anaesthesia characterized by rapid onset, short duration and freedom from excitatory side-effects, and both produced a degree of respiratory depression at larger doses. Hypotensive effects in pigs and therapeutic indices in mice were also similar. The hypnotic potency in mice of ICI 35 868 was 1.8 times greater than that of thiopentone. The anaesthetic profile of ICI 35 868 differed from that of thiopentone in that repeated doses could be given without significantly prolonging recovery time, complete recovery from a single dose occurred more rapidly, no tissue damage occurred following perivascular or intra-arterial injection and better reflex depression was obtained in mice at equipotent doses.

In this study a standard injection time was used in mice and a finite period of sleep specified in the calculation of HD_{50} values. These factors probably account for the lower therapeutic indices obtained with standard agents (table I) in comparison with those found by Child and others (1971). When a faster rate of injection was used in the assessment of speed of induction it was found that a much smaller dose of ICI 35 868 was required to cause the same effect. Although the other standard agents examined showed a similar change, only in the case of propanidid, another rapidly metabolized agent, did the magnitude of the effect approach that seen with ICI 35 868. This suggests that the dose requirement and speed of onset of anaesthesia in man with ICI 35 868 will be significantly affected by changes in the rate of injection. With a slow rate of administration, the effect of metabolism occurring during the course of an injection may limit the rate of increase in the blood concentration of the agent. Experiments in rats using whole-body autoradiographic techniques have demonstrated the presence of metabolic products of ICI 35 868 in the liver 30 s after i.v. injection (Rhodes and Longshaw, 1977).

The e.e.g. changes produced by ICI 35 868 in the rat indicate that the compound can produce profound, but rapidly reversed, depression of cerebral activity at doses close to the median hypnotic dose. This suggests that the dose–response curve for the cerebral depressant effect of ICI 35 868 is likely to be steeper than that obtained with the barbiturates with the result that little hypnosis is likely to be seen as the blood concentration decreases to less than that required to produce unconsciousness.

The combination of ICI 35 868 with drugs used for pre-anaesthetic medication, inhalation agents, and neuromuscular blocking drugs did not demonstrate any unexpected interactions. The movement noted in one cat at the time of administration of pancuronium was attributed to an inadequate level of anaesthesia, but may have been a manifestation of an initial stimulating action of pancuronium similar to that which has been described in a proportion of cats on the first administration of tubocurarine or gallamine (Payne, 1961).

Highly lipophilic compounds like ICI 35 868 were not previously examined in tests for anaesthetic activity because of their insolubility in aqueous solution. The availability of Cremophor EL as a solubilizing agent has removed this obstacle and has allowed the properties of ICI 35 868 to be examined in animals and in preliminary clinical investigations. An early study in man (Kay and Rolly, 1977) concluded that ICI 35 868 appeared to be a clinically effective induction agent with pain after injection being the only side-effect seen. This side-effect had not been predicted from studies in animals.

Should further work in man confirm that ICI 35 868 has a desirable anaesthetic profile, it is hoped that an alternative formulation can be developed which would be more acceptable for wider clinical use.

ACKNOWLEDGEMENTS

I wish to thank Mrs S. C. Hunter, Mr A. Jamieson and Mr S. Strong for their skilled technical assistance. I am also grateful to Mr J. R. Pateman, who performed the e.e.g. studies.

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ETUDES DE L'ACTIVITE ANESTHESIANTE D'ICI 35 868 SUR LES ANIMAUX

RESUME

On a procédé à des études sur une plage d'espèces animales pour observer l'activité du nouvel agent anesthésiant ICI 35 868, administré par voie intraveineuse. Il s'agit d'un composé sans aucune relation avec les agents barbituriques, eugéniques ou stéroïdes utilisés couramment. Certaines propriétés d'ICI 35 868 ressemblent à celles du thiopentone, en ce sens qu'il s'agit d'un agent ayant une action rapide qui provoque une anesthésie de courte durée, sans effets secondaires excitatoires. Ces deux agents ont un indice thérapeutique similaire et produisent des effets respiratoires et cardiovasculaires équivalents. Chez la souris, ICI 35 868 est 1,8 fois plus actif que le thiopentone en tant qu'agent hypnotique. Néanmoins, le profil anesthésique d'ICI 35 868 diffère de celui du thiopentone, en ce sens que la récupération est rapide même après des administrations répétées, qu'aucun dégât n'est causé aux tissus par les injections périvasculaires ou intra-artérielles et qu'un plus grand réflexe dépressif et des variations encéphalographiques plus profondes sont produites à des doses équivalentes. On a trouvé que ce nouvel agent était compatible avec une grande variété de médicaments utilisés comme médications pré-anesthésiantes, en inhalations anesthésiantes et avec les médicaments de blocage neuromusculaire.

TIERSTUDIEN DER ANÄSTHETISCHEN AKTIVITÄT VON ICI 35 868

ZUSAMMENFASSUNG

Die Aktivitäten eines neuen intravenösen Anästhesiemittels, ICI 35 868, nicht verwandt mit gegenwärtig benutzten Barbituraten, Eugenol oder Steroiden, wurde bei verschiedenen Tieren untersucht. Einige Eigenschaften der Droge ähneln denen von Thiopenton darin, dass es sich um ein rapide wirkendes Mittel handelt, das Anästhesie von kurzer Dauer und ohne erregende Nebenerscheinungen bewirkt. Beide Mittel haben einen ähnlichen therapeutischen Index und bewirken ahnliche kardiovaskuläre und respiratorische Effekte. Bei Mausen ist ICI 35 868 um 1,8 mal wirksamer als Thiopenton. Trotdem unterscheidet sich das anästhetische Profil von ICI 35 868 von Thiopenton darin, dass die Erholung nach wiederholten Dosen rapide ist, dass durch perivaskulare oder intraarterielle Injektionen keine Gewebsbeschädigung entsteht, und dass bei gleichstarken Dosen ICI 35 868 eine stärkere Reflexunterdrückung und profundere elektroenzephalographische Veränderungen bewirkt werden. Dieses neue Mittel hat sich als verträglich mit einer grossen Auswahl anderer Drogen erwiesen, die für Vornarkosebehandlung verwendet werden, ebenso wie mit Einatmungs-Narkosemitteln und mit neuromuskularen Blockierungsdrogen.

ESTUDIOS EN ANIMALES DE LA ACTIVIDAD ANESTESICA DEL ICI 35 868

SUMARIO

Se ha examinado la actividad de un nuevo agente anestésico intravenoso, el ICI 35 868, en una gama de especies animales; este compuesto no está relacionado con los agentes barbitúricos, eugenol, ni esteroides actualmente en uso. Ciertas propiedades del ICI 35 868 se asemejan a las de la tiopentona, respecto a que es un agente de rápida acción que produce anestesia de corta duración y sin efectos secundarios de excitación. Ambos agentes poseen un índice terapéutico similar y producen efectos cardiovasculares y respiratorios equivalentes. En lo que respecta al ratón, el ICI 35 868 es un hipnótico 1,8 veces más potente que la tiopentona. No obstante, la configuración anestésica del ICI 35 868 difiere de la tiopentona en que su recuperación es rápida después de repetidas administraciones, no se produce daño alguno a los tejidos a causa de inyecciones perivasculares o intraarteriales y a igualdad de potencia de las dosis se produce una mayor depresión de reflejos y cambios electroencefalográficos más profundos. Este nuevo agente ha demostrado ser compatible con una amplia gama de drogas usadas en medicación preanestésica, anestésicos de inhalación y drogas de bloqueo neuromuscular.

Br. J. Anaesth. (1980), **52**, 743

PHARMACOKINETICS IN LABORATORY ANIMALS OF ICI 35 868, A NEW I.V. ANAESTHETIC AGENT

H. K. ADAM, J. B. GLEN AND P. A. HOYLE

SUMMARY

Blood concentrations of ICI 35 868 have been determined in rat, pig, rabbit and cat after single i.v. injections. In all species the initial distribution volume was greater than blood volume and the overall distribution volume was large. Half-lives of the distribution phase were extremely short (1–6 min) and the terminal half-lives were also short (16–55 min). In all species examined a correlation existed between the systemic blood concentration of ICI 35 868 and duration of sleep, with concentrations in the range 1–4 μg ml^{-1} being effective in producing unconsciousness. No changes in pharmacokinetics or in the effective concentration occurred on repeated administration or after infusion.

There are several reports on the possibility of using i.v. anaesthetic agents for both induction and maintenance of anaesthesia (du Cailar, 1972; Breimer et al., 1975; Savege et al., 1975; Sear and Prys-Roberts, 1979). Work aimed at the development of new i.v. agents has concentrated on compounds which are eliminated from the body rapidly.

A review of recently introduced i.v. agents pointed out the importance of understanding their pharmacokinetics (Ghoneim and Korttila, 1977). We describe the pharmacokinetics in laboratory animals of ICI 35 868, a new i.v. anaesthetic agent, and relate systemic blood concentrations of this agent with the pharmacological effects produced.

MATERIALS AND METHODS

ICI 35 868 was administered as a 2% formulation in 10% Cremophor in saline to all species. The compound was administered to rats (ICI Alderley Park Wistar-derived albino strain) via the tail vein and blood samples obtained by cardiac puncture; to pigs (young white Large White × Landrace) via an indwelling jugular vein cannula and samples obtained from an arterial cannula; to rabbits (Dutch) via an ear vein and samples obtained from an indwelling jugular vein cannula; and to cats (domestic) via the cephalic vein and samples obtained from an indwelling jugular cannula.

Animals were given single doses by i.v. injection over 30 s. Doses administered were as follows: rats and rabbits 7.5 and 15 mg kg^{-1}, pigs 5 and 10 mg kg^{-1} cats 5 and 15 mg kg^{-1}. Blood samples were obtained before dosing and at various times up to 2 h after administration. Samples were also obtained from rats (10 and 15 mg kg^{-1}) and pigs (5 and 7.5 mg kg^{-1}) which had received these doses once daily for 30 successive days. For infusion studies pigs received either a constant infusion at a rate of 24 mg kg^{-1} h^{-1} or an infusion rate adjusted to maintain a light level of surgical anaesthesia. In both cases infusion was begun immediately after an induction dose of 5 mg kg^{-1}.

Analysis of ICI 35 868 *content*

To 1 ml of oxalated whole blood was added dipotassium hydrogen phosphate 0.1 mol litre^{-1}, followed by cyclohexane/n-butanol (95 : 5 v/v) 4 ml. The mixture was shaken for 10 min and the phases separated by centrifugation. An aliquot of the organic phase was assayed in a spectrofluorimeter (Perkin-Elmer MPF2A) by examining the emission at 310 nm produced by an excitation wavelength of 265 nm. Unknowns were quantified by comparison of the peak heights obtained with those from a standard series prepared by adding known amounts of ICI 35 868 to control blood. The limit of detection of this procedure was ICI 35 868 0.2 μg ml^{-1} whole blood.

RESULTS

All animal species showed similar pharmacokinetic profiles. Figure 1, which shows the profile obtained in the rat after a single i.v. dose of ICI 35 868 15 mg kg^{-1}, is typical. There was a very rapid initial distribution phase, followed by a slower

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0007–0912/80/080743-04 $01.00

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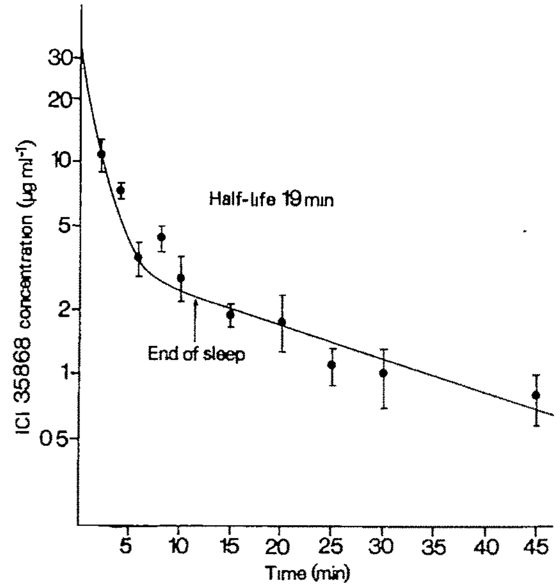

FIG. 1, Blood concentrations of ICI 35 868 in rats (three at each time point ±SEM) after a single i.v. dose of ICI 35 868 15 mg kg^{-1}.

elimination phase. Treatment of the data according to the two-compartment model of Riegelman, Loo and Rowland (1968) allows calculation of V (the apparent volume of distribution of the "central compartment"), V^{β} (the overall apparent volume of distribution) and $T_{\frac{1}{2}}^{\alpha}$, and $T_{\frac{1}{2}}^{\beta}$, the half-lives of the two portions of the biexponential curve.

The results derived from figure 1 are included in table I, with the data obtained in the other animal species examined. In all cases the results were derived from the greater dose since the results from the smaller doses did not permit full pharmacokinetic evaluation because of inability to follow concentrations long enough to define the terminal half-life with any degree of confidence. However, it was apparent that, apart from the cat, no major change in pharmacokinetics occurred in any species between the two doses. In all cases $T_{\frac{1}{2}}^{\alpha}$ was extremely short with a range of 1.1–5.8 min. The terminal elimination half-life ranged from 16 min in the rabbit to 55 min in the cat. The apparent volumes of distribution of the central compartment (V) ranged from 33% in the rabbit to 90% in the cat. Overall distribution volumes were larger, ranging from 133% in the cat to 275% in the pig.

TABLE I. *Pharmacokinetic parameters of ICI 35 868 in laboratory animals. Results are mean ± SEM of each parameter from individual animals, except in the rat, where they are derived from groups of animals at each time point (see figure 1). V^{β} calculated from the area under the curve according to Gibaldi, Nagashima and Levy* (1969)

Species	V (% body wt.)	V^{β} (% body wt.)	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	No. animals studied
Rat	43	250	1.1	19	30
Pig	82±14	275±44	3.0±1.1	40±1	3
Rabbit	33±4	155±33	1.9±0.3	16±1	4
Cat	90±16	133±19	5.8±0.4	55±3	4

No major change in the pharmacokinetics in rat or pig occurred after daily dosing for 30 consecutive days.

In all species a measure of duration of sleep after dosing was made and the systemic concentration of ICI 35 868 at the end of this period was determined (table II). In each species the concentration was independent of dose or numbers of doses and was characteristic of that species. With the exception of the rabbit, which seems less sensitive, the concentration range required to achieve sleep in laboratory animals was 1–4 μg ml^{-1}.

TABLE II. *Mean waking concentrations of ICI* 35 868 *in laboratory animals*

Species	Concentration (μg ml^{-1})	Number of studies
Rabbit	7.2	4
Cat	4.3	4
Rat	2.8	5
Pig	1.1	3

The concentrations of ICI 35 868 found in a pig in which sleep had been maintained for 2 h by continuous infusion of ICI 35 868 24 mg kg^{-1} h^{-1} are presented in figure 2 (●). Also included in this figure are the results obtained in this species after a single i.v. injection (fig. 2, ○). The terminal half-lives were similar. Head lift in the animal in the infusion study occurred at a concentration of about ICI 35 868 3 μg ml^{-1}. In a similar infusion study a lighter level of anaesthesia was maintained by infusion rates between 8.2 and 16.7 mg kg^{-1} h^{-1}. In this animal, anaesthesia was maintained at concentrations in the range 3–5 μg ml^{-1} and head lift occurred 6 min after stopping the infusion when the systemic concentration was less than 2 μg ml^{-1}.

DISCUSSION

Our studies show that a correlation exists between systemic blood concentrations of ICI 35 868 and the

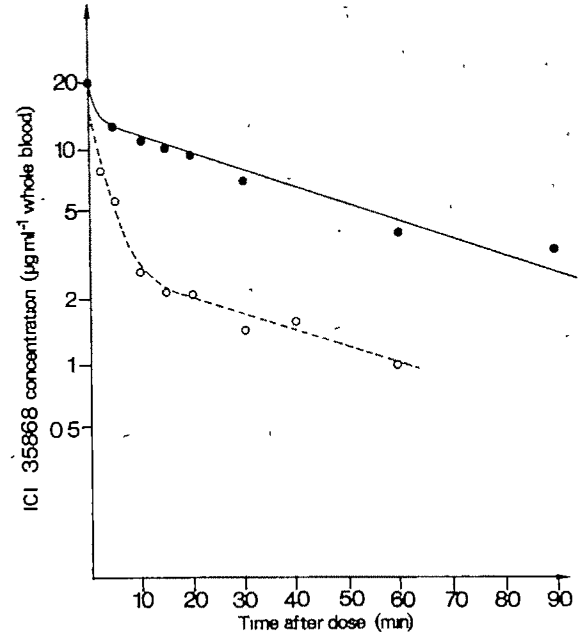

FIG. 2. Concentrations of ICI 35 868 in pig blood after 2 h infusion at 24 mg kg^{-1} (time zero = end of infusion) (●); and after a single i.v. dose of 10 mg kg^{-1} (○).

effect of this agent, as measured by the duration of sleep in laboratory animals. Hence the major factor influencing the duration of action and effect on maintenance will be the pharmacokinetic profile in the species in question. It has also been shown that no changes in effect or pharmacokinetics occur on continued or repeated administration of ICI 35 868 to animals. Thus there were no evidence of acute tolerance or accumulation.

The rapid onset of action and recovery can be explained in pharmacokinetic terms. It is clear from table I that, in all animal species examined, the initial distribution volume was greater than blood volume alone. Thus, the "central compartment" can be considered to contain well-perfused organs such as brain. This has been confirmed by autoradiography (Rhodes and Longshaw, 1977). In the initial distribution period (α-phase), redistribution to other parts of the body was extremely rapid, resulting in a steep decline in systemic and brain concentrations. The total apparent volume of distribution was large, as might be expected for a lipophilic drug. After distributional equilibrium had been attained, metabolic clearance from the body was still rapid with elimination half-lives in the range 16–55 min.

Correlating the anaesthetic effect with the systemic blood concentration assumes that the latter is in dynamic equilibrium with the site of action. Although the initial apparent volume of distribution may include brain, and the whole body autoradiographic studies cited above showed that brain concentrations of volatile material, which was considered to be unchanged drug, decreased very rapidly, some questions must remain as to whether venous blood concentrations reflect concentrations in the "biophase". This is especially true for ICI 35 868 with which the initial distribution phase is rapid and in some species, such as rabbit, awakening occurred during the α-phase. Infusion studies should allow a closer approximation of dynamic equilibrium between site of action and systemic concentrations. After infusion of ICI 35 868 to the pig the systemic concentrations at awakening were similar to those observed after acute administration, indicating that the values given in table II are proportional to biophase concentrations.

Several implications follow from these pharmacokinetic findings. First, the rate of administration of ICI 35 868 must be sufficiently rapid to compensate for the rapid redistribution from the brain to other parts of the body. Second, if recovery occurs during the α-phase, it will be extremely rapid. Finally, even if distributional equilibrium is achieved before recovery occurs, this will still be rapid because of the short terminal half-life.

If the agent is given by infusion, tissue equilibration will be approached. The effect of this is seen in figure 2 (●) where, in comparison with the single dose (fig. 2, ○), the α-phase was effectively shortened. This is because transfer of the drug between the central compartment and the tissues occurred throughout the infusion, resulting in a lower flux of the agent from the central compartment being required to establish tissue equilibration at termination of the infusion.

This examination of ICI 35 868 in animals has shown that it has a pharmacokinetic profile similar to Althesin (Child et al., 1972) and etomidate (Ambre et al., 1977), but markedly different from that of thiopentone (Brodie et al., 1950).

Although the newer agents discussed above have the desired pharmacokinetic properties required for short-term maintenance anaesthesia, exitatory phenomena have been noted with methohexitone and etomidate (Whitwam, 1978). ICI 35 868 possesses suitable pharmacokinetic properties and produces fewer excitory effects than Althesin or methohexitone

(Glen, 1980) in laboratory animals. Work is in progress to study its pharmacokinetics in man.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the valuable technical assistance given by Mr M. B. Cosgrove, Mrs S. C. Hunter and Mr D. Jones and staff.

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PHARMACOCINETIQUE SUR DES ANIMAUX DE LABORATOIRE DE ICI 35 868—NOUVEL AGENT ANESTHESIANT INTRAVEINEUX

RESUME

Les concentrations d'ICI 35 868 dans le sang ont été déterminées sur des rats, cochons, lapins et chats après des injections intraveineuses uniques. Sur toutes ces espèces, le volume de répartition initial a été plus fort que le volume sanguin total et le volume de répartition d'ensemble a été important. Les demi-vies de la phase de répartition ont été extrêmement courtes (1–6 min) et les demi-vies terminales ont également été courtes (16–55 min). Sur toutes les espèces examinées, il y a eu une corrélation entre la concentration d'ICI 35 868 dans le sang systémique et la durée du sommeil, les concentrations dans la plage de 1–4 μg ml^{-1} étant efficaces pour provoquer la perte de connaissance. Il n'y a eu aucun changement dans la pharmacocinétique ou dans la concentration effective après une administration répétée ou après une infusion.

DIE PHARMAKOKINESE VON ICI 35 868, EINEM NEUEN INTRAVENÖSEN NARKOSEMITTEL BEI LABORATORIUMSTIEREN

ZUSAMMENFASSUNG

Die Blutkonzentrationen von ICI 35 868 in Ratten, Schweinen, Kaninchen und Katzen wurden nach intravenosen Einzelinjektionen bestimmt. Bei allen Tieren war das anfangliche Verteilungsvolumen grösser als das Blutvolumen, und das Gesamtverteilungsvolumen war gross. Die Halbwertzeiten der Verteilungsphase waren äusserst kurz (1–6 min), und die Endhalbwertzeiten ebenfalls (16–55 min). Bei allen untersuchten Tieren bestand eine Korrelation zwischen der systemischen Blutkonzentration von ICI 35 868 und der Schlafdauer, wobei Konzentrationen im Bereich 1–4 μg ml^{-1} wirksam Bewusstlosogkeit hervorriefen. Keine pharmakokinetischen Änderungen oder Konzentrationsänderungen erfolgten bei wiederholter Verabreichung oder bei Infusion.

FARMACOCINETICAS EN ANIMALES DE LABORATORIO, DEL ICI 35 868 QUE ES UN NUEVO AGENTE ANESTESICO INTRAVENOSO

SUMARIO

Se han determinado concentraciones de ICI 35 868 en la sangre de ratas, cerdos, conejos y gatos, después de una única inyección intravenosa. El volumen inicial de la distribución fue, para todas las especies, superior al volumen de sangre, y el volumen de la distribución global fue cuantioso. Las media-vidas de la fase de distribución fueron extremadamente cortos (1–6 min) y la media-vida terminal fue también de corta duración (16–55 min). En todas las especies que se examinaron existió una correlación entre la concentración sistémica de ICI 35 868 en la sangre y la duración del sueño, siendo efectivas concentraciones comprendidas dento de la gama 1–4 μg ml^{-1} para producir estados inconscientes. No se produjeron cambios en las farmacocinéticas ni en la concentración efectiva, bajo la administración sucesiva ni después de una infusión.

Br. J. Anaesth. (1980), **52**, 747

EFFECT OF EXPERIMENTAL CHOLESTASIS ON NEUROMUSCULAR BLOCKING DRUGS IN CATS

P. WESTRA, M. C. HOUWERTJES, A. R. DE LANGE, A. H. J. SCAF, F. R. HINDRIKS AND S. AGOSTON

SUMMARY

Pancuronium, Org 6368 and gallamine were compared in control cats and in cats with experimental cholestasis. A decrease in the plasma clearance and a prolongation of neuromuscular blockade with Org 6368 and pancuronium were found in the latter; no significant difference was detected in the biotransformation pattern of Org 6368 and pancuronium compared with controls. Inhibition of hepatic uptake of Org 6368 and pancuronium in extrahepatic cholestasis might explain the significant alterations in the pharmacokinetics of the two steroid neuromuscular blocking drugs. The pharmacokinetics of gallamine were normal during cholestasis. The results suggest that, under pathological conditions involving increased plasma concentrations of bile salts, neuromuscular blocking agents that are cleared from the plasma by the liver may have an impaired hepatic uptake and consequently a prolonged duration of action.

Cholestasis is associated with a variety of metabolic abnormalities some of which, for example jaundice and increased plasma bile salt concentrations with steatorrhea, are the direct result of the failure of bilirubin and bile salt secretion into bile. However, certain other phenomena associated with extrahepatic cholestasis are more difficult to explain. Examples are the increased duration of action of hexobarbitone in rabbits with obstructive jaundice (McLuen and Fouts, 1961) and a prolongation of the sleeping time caused by the steroid anaesthetic Althesin (Novelli, Marsili and Lorenzi, 1975). Ward, Adu-Gyamfi and Strunin (1975) reported difficulties in antagonizing the effects of pancuronium in two patients with severe obstructive jaundice. Significant changes in the elimination of pancuronium which resulted in a prolonged neuromuscular blockade in patients with total biliary obstruction, were reported by Somogyi, Shanks and Triggs (1977).

The liver takes up many drugs from the bloodstream and plays an important role in the metabolism and excretion of these compounds. Interference with either of these processes will affect the pharmacokinetic pattern of such drugs. This may have clinical consequences such as alterations in their duration of action.

In the case of the neuromuscular blocking drugs tubocurarine (Cohen, Brewer and Smith, 1967; Meijer and Scaf, 1968; Meijer et al., 1979), pancuronium (Agoston et al., 1973; Buzello, 1975) and hexafluorenium (Meijer, Vermeer and Kwant, 1971), hepatic uptake and secretion appear to be major factors in determining the plasma concentrations. In the cat, hepatic uptake is an important factor in the plasma clearance of a number of steroid neuromuscular blocking agents, such as pancuronium, dacuronium and Org 6368 (Agoston, Kersten and Meijer, 1973; Agoston et al., 1977).

We investigated the fate of non-depolarizing neuromuscular blocking agents in extrahepatic cholestasis. Three compounds, known to differ considerably in their elimination pathways (i.e. renal or biliary), were studied:

Org 6368, the bisquaternary ammonium compound (2β,16β,-dipiperidino-5α-androstan-3α-ol- acetate dimethobromide) differing from pancuronium only in lacking the acetate group at C17 position in the steroid skeleton and having a short duration of action in the cat (Sugrue and Duff, 1973), mainly as a result of a rapid hepatic uptake (Agoston et al., 1977);

gallamine triethiodide, which in dog and man is predominantly eliminated by the kidneys (Mushin et al., 1949; Feldman, Cohen and Golling, 1969; Agoston et al., 1978);

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0007-0912/80/080747-11 $01.00

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pancuronium, which in cat and man is eliminated by both urinary and biliary routes (Agoston, Kersten and Meijer, 1973; Agoston et al., 1973).

The dynamics and kinetics of these compounds were investigated in cats with experimentally induced cholestasis and compared with control animals.

MATERIALS AND METHODS

Operative procedures

Ligation of the bile duct was performed under anaesthesia with sodium pentobarbitone anaesthesia (40 mg kg^{-1} i.p.), or 2% halothane in 33% oxygen in nitrous oxide after ketamine 50–100 mg i.m. An endotracheal tube was inserted and the lungs ventilated artificially. A mid-line abdominal incision was made, and the common bile duct was doubly ligated with Perma-Hand Seide 4–0 suture approximately 1 cm from the point of entry to the duodenum. The cystic duct was doubly ligated at the base of the gall-bladder, after which the incision was closed with Perma-Hand Seide. The entire operation took less than 30 min. After the operation, all animals were treated with ampicillin 100–200 mg, i.m. The obstruction of the bile ducts lasted 9–10 days. Sham-operated (all manipulations without ligation) and un-manipulated cats served as controls.

Animal experiments

All experiments were carried out in adult cats (2.8 ± 0.2 kg) of either sex under pentobarbitone anaesthesia (40 mg kg^{-1}, i.p. plus maintenance doses of 4 mg kg^{-1} i.v.). After orotracheal intubation, artificial ventilation with air through a cuffed Magill tube of 5.5 mm external diameter was maintained with a Braun respirator type 1955, set at a rate of 30 b.p.m. and a tidal volume of 10 ml kg^{-1}. A polythene cannula was introduced into the common bile duct and in the control animals the cystic duct was ligated. Through a low abdominal incision, the urethra and the urinary bladder were visualized and the urethra was cannulated. In order to check the general condition of the cat, e.c.g. (ECG-Pulse Monitor, MS-35; Electrodyne Co. Inc., U.S.A.) and mean arterial pressure (Statham P23D6-transducer; KWS 3085 HSE Electro-Manometer) were monitored. Body temperature was kept constant at 36–38 °C by heating the operating table. Rectal temperature was measured with a thermistor (Electrolaboriet, Copenhagen). To replace fluid loss, glucose (2.5%) and saline (0.45%) were infused through a polythene cannula in the external jugular vein. Neuromuscular studies (isometric twitch tension) were performed on the tibialis anterior muscle which was stimulated through the common peroneal nerve with supramaximal square-wave pulses of 0.2-ms duration at a frequency of 0.1 Hz. The stimulus was supplied from a Grass S88 stimulator and SIU 5 stimulus isolation unit. The tendon of the tibialis anterior muscle was connected to a load cell (UL4-20, Statham), attached to a force-displacement transducer (UC3 Gold Cell, Statham), mounted securely on a Braun–Schuster myograph. The signal was amplified by a Hottinger–Baldwin amplifier (Messtechniek, Darmstadt) and muscle contractions were continuously recorded on a MFE two-channel polygraph (d.c. to 40 Hz, full scale). Pancuronium 0.3 mg kg^{-1}, Org 6368 1.5 mg kg^{-1} and gallamine 5.0 mg kg^{-1} were injected i.v. over 5 s. Blood, urine and bile samples were collected at fixed intervals. Eight hours after administration of the drugs, the experiments were terminated by removing the liver within 2 min. All samples were deep frozen for later chemical analysis.

Neuromuscular studies

The time to the onset of maximum block was defined as the time which elapsed from the injection until the twitch had reached its minimum value. For the duration of action, two indices were used:

(a) time from administration of the drug until the return of the twitch tension to 50% of control value (duration 50);

(b) time from administration of the drug until reversal to 90% of control tension (duration 90).

Recovery time is defined as the time from the minimum value before recovery to 25, 50 and 75% recovery of control twitch tension (recovery 25, 50, 75). The recovery rate is the time from 25 to 75% recovery of control twitch tension (recovery rate 25–75) (fig. 1).

Analysis of the quaternary ammonium compounds and of some physiological plasma constituents

Determinations of plasma concentrations of total bilirubin, direct bilirubin, total cholesterol, glutamic–pyruvic transaminase, alkaline phosphatase, urea and creatinine of the cats were performed with an Automatic Chemical Analyzer of E. I. du Pont de Nemours & Co. (Inc.), Wilmington, DE 19898. Enzyme activities are expressed in international units per litre (iu $litre^{-1}$).

Total bile salt concentrations in the plasma were measured with an enzymatic kit for spectrofluorimetric end-point determinations (Sterognost-3α Automated, Nyegaard & Co. AS, Oslo, Norway).

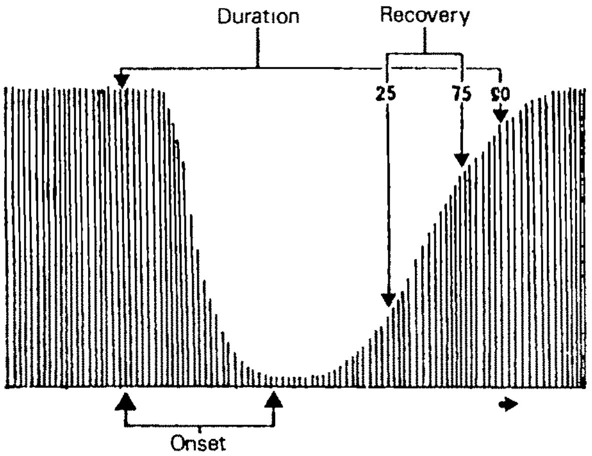

FIG. 1. Characterization of the neuromuscular blockade.

3α-Hydroxysteroid dehydrogenase transforms the 3α-hydroxyl group on steroids of the C19, C21 and C24 series into their corresponding keto forms, by which NADH is generated from NAD (Mashige, Imai and Osuga, 1976; Osuga et al., 1977). The reduction equivalents of NADH are transferred to the fluorogen resazurin by the enzyme diaphorase, with formation of the fluorophore resorufin. This substance is measured with an Aminco–Bowman Spectrofluorimeter (Am. Instr. Comp.). Excitation wave length was 565 nm and emission wave length 580 nm.

Spectrofluorimetric determinations of pancuronium Org 6368 and gallamine and thin-layer chromatography of these bis(tris)-quaternary ammonium compounds and metabolites have been described in detail elsewhere (Kersten, Meijer and Agoston, 1973; Agoston et al., 1977; Agoston et al., 1978).

The fluorimetric method for bisquaternary ammonium compounds does not discriminate between pancuronium, Org 6368 and their deacetylated metabolites(s). Chromatographic quantification of the bisquaternary ammonium compounds in bile and liver homogenate as described previously (Kersten, Meijer and Agoston, 1973; Agoston et al., 1977) was improved by mixing the samples (1 ml) with 0.1 ml of a saturated copper sulphate solution and removing the precipitated material by centrifugation. The supernatant was used for further chromatographic procedures.

Conjugation

To investigate a possible conjugation of Org 6368 or metabolite(s) with sulphate or glucuronic acid liver homogenates of control cats receiving Org 6368 1.5 mg kg^{-1} were analysed.

Sulphate conjugation: to 2 ml of liver homogenate (1 mg of tissue in 1 ml Krebs-bicarbonate) 1 ml of Tris-buffer 2 mol $litre^{-1}$ ($pH = 7.4$) and 100 μlitre partially purified bacterial aryl sulphatase solution (Sigma, St Louis, U.S.A.) were added.

Glucuronidation: to 2 ml of liver homogenate, 1 ml of sodium acetate-buffer 0.5 mol $litre^{-1}$ ($pH = 6.0$) and 100 μlitre of highly purified bacterial glucuronidase solution (Boehringer, Mannheim, West Germany) were added. The mixtures were adjusted to 15 ml with distilled water and incubated for 2.5 h at 37 °C. The same liver homogenates without addition of the enzyme preparations served as controls. Fluorescence of non-enzyme treated and enzyme-treated livers containing Org 6368 or its metabolite(s) were compared. This method is based on the assumption that the polar conjugates of the metabolite(s) of Org 6368 will not be extracted with Rose–Bengal into the chloroform phase (Buzello, 1975).

Statistics

All values are given as mean ± SEM. Statistical significance was tested using either the paired or the unpaired Student's t test with a 95% significance level.

Pharmacokinetic calculations

The disposition of neuromuscular blocking drugs can be described mathematically by a two- or three-compartment open model (Gibaldi, Levy and Hayton, 1972; McLeod, Watson and Rawlins, 1975; Somogyi, Shanks and Triggs, 1976, Miller et al., 1979).

Plasma clearance curves were fitted using a computerized program which, after balanced iterative peeling of the curves, yields straight regression lines of log plasma concentration *v.* time, using the least squares method. Pharmacokinetic model-parameters, such as steady-state volume of distribution (V^{ss}), volume of central compartment (V_1) and plasma clearance (Cl) were calculated according to Wagner (1976).

RESULTS

Clinical chemistry

There was no impairment of renal glomerular filtration in the cats with extrahepatic cholestasis, as judged by normal plasma concentrations of creatinine and urea. The liver function tests revealed significant increases of the enzymes alkaline phosphatase (AP) and glutamic-pyruvic transaminase (GPT) in the jaundiced cats. Significant increases in the plasma concentrations of total cholesterol and total bilirubin were observed. Approximately 60% of the total bilirubin in the plasma was present as a glucuronide conjugate.

Total bile salt concentrations in plasma, after 9–10 days experimental cholestasis, were increased more than 100-fold as compared with control. Relief of biliary obstruction by cannulation of the common bile duct caused a linear decay of the plasma bile salt concentration, indicating saturation elimination kinetics. After 7 h the concentration was about half the initial value (fig. 2). Total cholesterol concentrations had returned to baseline after 480 min and total bilirubin plasma concentration was decreased by about 40% at that time (table I).

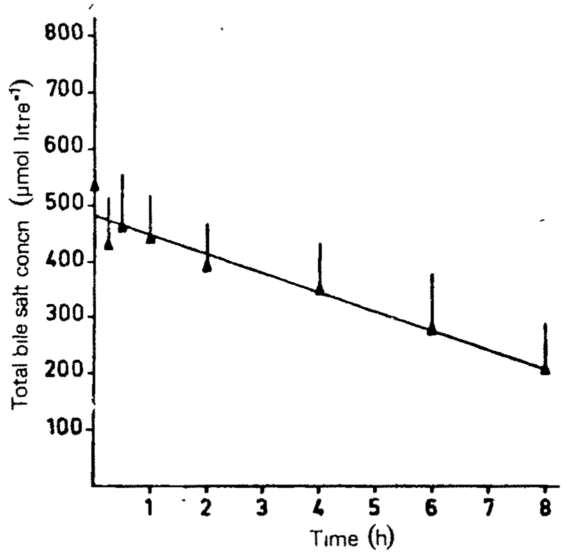

FIG. 2. Total bile salt concentration in plasma after relief of the biliary obstruction ($n = 12$). Mean ± SEM.

Pharmacodynamics

The pharmacodynamic indices defining the neuromuscular blockade of Org 6368 in cats with experimental cholestasis differed clearly from those of the control animals, except for the time of onset of action. The same is true, but to a lesser extent, for pancuronium (table II).

Cholestasis produced a 5.5-fold prolongation of the duration to 90% twitch recovery with Org 6368 compared with controls; for pancuronium this prolongation was only 1.6-fold (fig. 3). In contrast, cholestasis had no influence on the dynamics of gallamine (table II). Also, no significant differences between un-manipulated control cats and sham-operated cats were found for Org 6368 in this respect (table II).

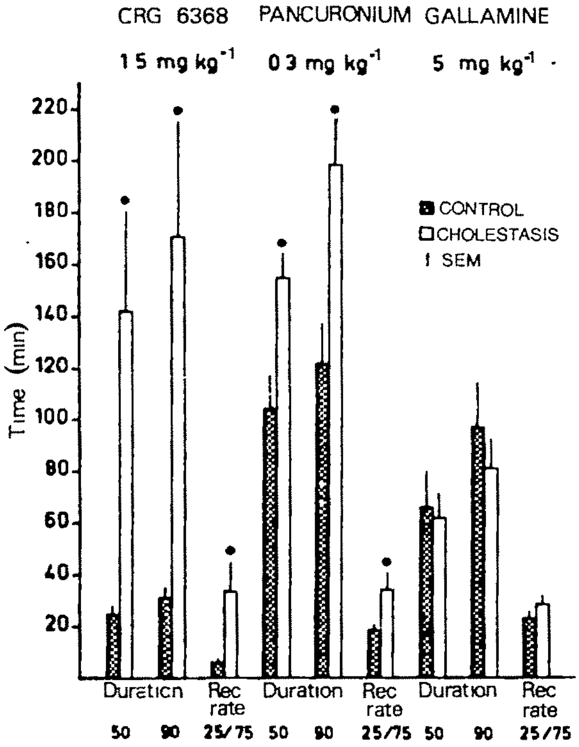

FIG. 3. Duration to 50 and 90% recovery of control twitch tension and the recovery rate from 25 to 75% of control twitch tension for Org 6368, pancuronium and gallamine in control cats and cats with cholestasis. Mean ± SEM. * Significant difference from control.

Pharmacokinetics of Org 6368

The pharmacokinetic indices such as the half-lives ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$ and $T_{\frac{1}{2}}^{\gamma}$), the plasma clearance (*Cl*), the volume of central compartment (V_1) and the steady-state volume of distribution (V^{ss}) of the three quaternary ammonium compounds are given in table IV. For Org 6368, a considerable decrease in plasma clearance and significant increases of the distribution half-life $T_{\frac{1}{2}}^{\alpha}$ and of the elimination half-life $T_{\frac{1}{2}}^{\beta}$ were found in extrahepatic cholestasis (table IV, fig. 4).

The cumulative urinary excretion of Org 6368 (fig. 5) in extrahepatic cholestasis revealed a profound increase, from 10% to approximately 40% of the

TABLE I. *Analysis of plasma just before relief of the biliary obstruction ("0") and 480 min after administration of the drugs. Mean ± SEM. Figures in parentheses indicate range. * Significant difference from controls. AP = alkaline phosphatase; GPT = glutamic–pyruvic transaminase*

	Total bile salt (µmol litre⁻¹)	Total bilirubin (µmol litre⁻¹)	Direct bilirubin (µmol litre⁻¹)	Total cholesterol (mmol litre⁻¹)	AP (iu litre⁻¹)	GPT (iu litre⁻¹)	Urea (mmol litre⁻¹)	Creatinine (µmol litre⁻¹)
Control "0" min $n = 12$	1.7 ± 0.7 (0–4.1)	4 ± 1 (2–7)	3 ± 1 (0–7)	2.18 ± 0.21 (1.30–2.83)	18 ± 10 (0–81)	53 ± 7 (30–102)	8.2 ± 0.5 (5.9–11.6)	87 ± 6 (60–105)
Sham "0" min $n = 3$	0.7 ± 0.4 (0–1.2)	4 ± 1 (3–4)	0	2.80 ± 0.77 (1.55–4.19)	29 ± 20 (2–63)	56 ± 18 (23–83)	11.0 ± 0.2 (10.6–11.4)	88 ± 12 (70–110)
Cholestasis "0" min $n = 13$	521 ± 119* (81–794)	171 ± 29* (44–343)	105 ± 18* (30–216)	3.24 ± 0.26* (1.11–3.90)	103 ± 29* (51–169)	741 ± 98* (521–1550)	9.2 ± 0.9 (4.7–17.6)	88 ± 7 (80–115)
Cholestasis 480 min $n = 9$	212 ± 82* (0–422)	107 ± 25* (27–248)	62 ± 13* (14–133)	2.38 ± 0.29 (1.18–3.80)	—	—	—	—

TABLE II. *Quantification of neuromuscular blockade after i.v. administration of Org 6368, pancuronium and gallamine in control cats, sham-operated cats (only in case of Org 6368) and cats with cholestasis. Mean ± SEM. * Significant difference from controls*

	Drug (µg kg⁻¹)	Block (%)	*n*	Onset (min)	Duration (min)		Recovery (min)			Recovery rate (min)
					50	90	25	50	75	25–75
Control	Org 6368 1500	100	5	0.63 ± 0.07	24.65 ± 3.42	30.81 ± 4.08	4.33 ± 0.56	6.87 ± 1.00	10.50 ± 1.72	6.10 ± 1.17
Sham	Org 6368 1500	100	3	0.56 ± 0.06	18.80 ± 2.39	24.22 ± 3.47	4.05 ± 0.62	6.06 ± 1.03	8.50 ± 1.69	4.50 ± 1.07
Cholestasis	Org 6368 1500	100	5	0.56 ± 0.04	142.20* ± 38.64	170.72* ± 44.97	18.90* ± 5.08	35.50* ± 9.51	50.17* ± 25.08	33.38* ± 11.26
Control	Pancuronium 300	100	5	0.77 ± 0.04	104.10 ± 13.26	121.83 ± 15.78	14.64 ± 1.77	23.77 ± 3.08	33.17 ± 3.95	18.53 ± 2.59
Cholestasis	Pancuronium 300	100	4	0.75 ± 0.05	154.71* ± 10.34	199.13* ± 17.89	26.59* ± 3.09	39.81* ± 4.31	60.87* ± 5.95	34.28* ± 7.04
Control	Gallamine 5000	100	5	0.77 ± 0.07	66.25 ± 13.39	96.99 ± 18.28	16.70 ± 2.15	27.58 ± 3.94	39.87 ± 4.62	23.17 ± 3.09
Cholestasis	Gallamine 5000	100	5	0.75 ± 0.05	61.68 ± 11.53	81.42 ± 11.32	18.05 ± 2.68	31.73 ± 3.94	46.37 ± 5.51	28.31 ± 3.51

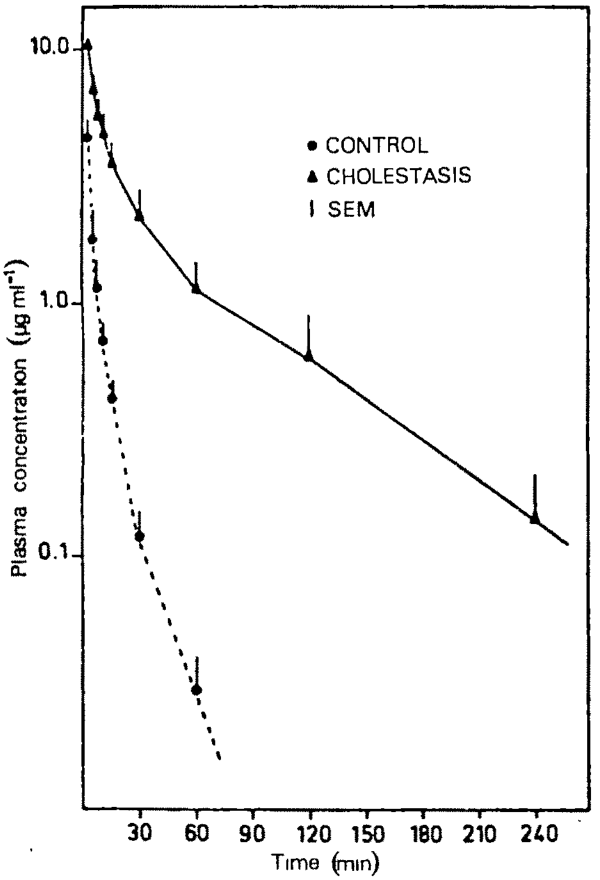

FIG. 4. Semilogarithmic plot of the mean plasma concentration–time profiles of Org 6368 in control cats ($n = 5$) and cats with cholestasis ($n = 5$).

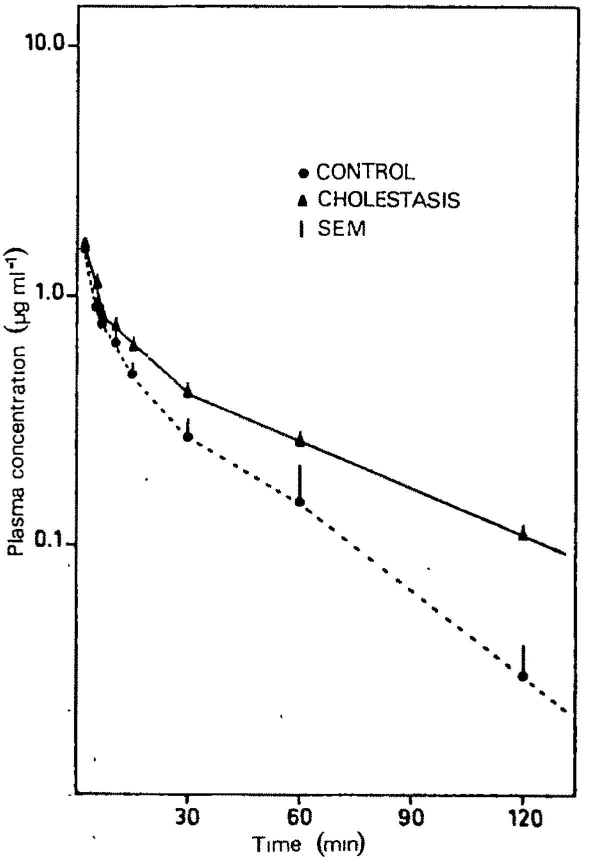

FIG. 6. Semilogarithmic plot of the mean plasma concentration–time profiles of pancuronium in control cats ($n = 5$) and cats with cholestasis ($n = 4$).

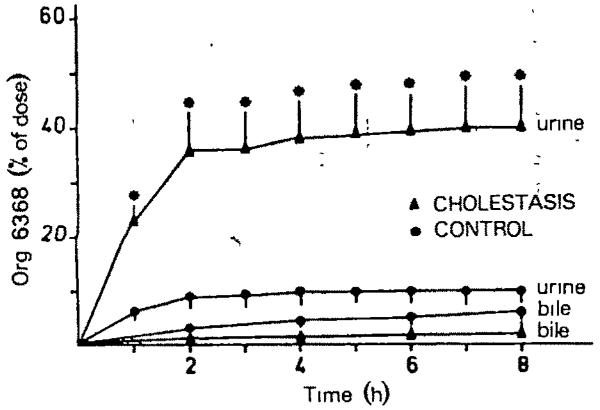

FIG. 5. Cumulative urinary and biliary excretion of Org 6368 and its metabolite in control cats ($n = 5$) and cats with cholestasis ($n = 5$). Mean ± SEM. * Significant difference from control.

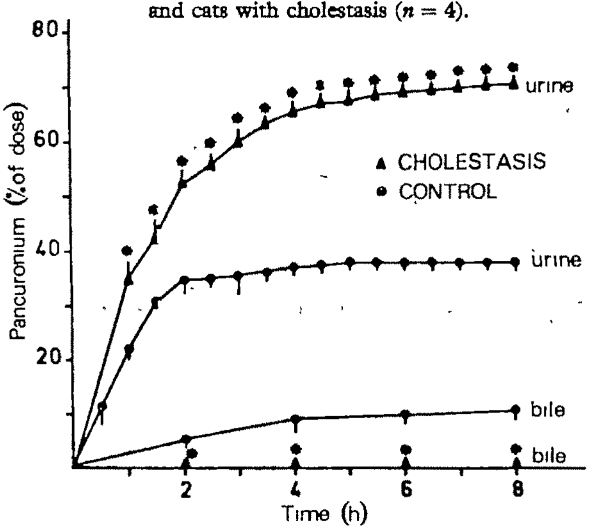

FIG. 7. Cumulative urinary and biliary excretion of pancuronium and its metabolites in control cats ($n = 5$) and cats with cholestasis ($n = 4$). Mean ± SEM. * Significantly difference from controls.

administered dose, compared with the control cats. No statistically significant differences were found for the biliary excretion and the liver content after 8 h for Org 6368 between extrahepatic cholestasis and the control cats (fig. 5, table III). The total recovery of Org 6368 from bile, urine and liver in extrahepatic cholestasis was significantly greater than in the control cats (table III). There were no statistical differences in kinetics between the un-manipulated control cats and the sham-operated cats for Org 6368 (tables III, IV).

Pharmacokinetics of pancuronium

The elimination half-life $T_{\frac{1}{2}}{}^{\beta}$ for pancuronium in extrahepatic cholestasis differed from that in the control cats (table IV, fig. 6).

Cumulative urinary excretion of pancuronium showed a 1.8-fold increase compared with control (fig. 7).

Pancuronium could not be detected in the bile of cats with cholestasis (fig. 7), while the liver content of pancuronium after 8 h was significantly less than in controls (table III). The total recovery from bile, urine and liver of pancuronium in extrahepatic cholestasis was significantly greater than in the control (table III).

Pharmacokinetics of gallamine

The pharmacokinetics for gallamine did not show significant differences between the group of cats with extrahepatic cholestasis and the control (tables III, IV, figs 8, 9).

Biotransformation

Thin-layer chromatography of urine, bile and liver samples of cats receiving Org 6368 was performed to obtain more information on biotransformation in extrahepatic cholestasis.

We found that, in extrahepatic cholestasis, Org 6368 is metabolized to its 3-hydroxy derivative to about the same extent as in control cats—approximately 60% of the administered dose after 8 h

TABLE III. *The mean percentage of the dose of neuromuscular blocking drug in the liver, bile and urine 8 h after i.v. administration of pancuronium, Org 6368 and gallamine in control cats, sham-operated cats (only in case of Org 6368) and cats with cholestasis. * Figures in parentheses indicate the approximate percentage of the compounds which are present in liver, bile and urine in the form of metabolite(s). — = not detectable; n.d. = not determined.*

	Pancuronium		Org 6368			Gallamine	
Time (h)	Control	Cholestasis	Control	Sham	Cholestasis	Control	Cholestasis
Liver 0–8	24.7 (–)*	13.1 (–)	55.0 (54.0)	56.4 (55.5)	49.0 (48.0)	5.2	11.3
Bile 0–2	5.1 (1.5)	0	3.1 (1.0)	n.d.	1.0 (0.5)	0.16	0.36
2–4	3.8 (1.0)	0	1.4 (0.6)	n.d.	0.4 (0.4)		
4–6	1.2 (0.9)	0	0.7 (0.4)	n.d.	0.5 (0.5)		
6–8	0.6 (0.6)	0	0.7 (0.3)	n.d.	0.4 (0.3)		
Urine 0–2	34.7 (0.2)	52.4 (3.5)	9.0 (1.0)	8.5 (2.3)	35.7 (7.9)	45.4	39.6
2–4	2.4 (0)	13.2 (3.8)	0.9 (0.3)	0.4 (0.1)	2.6 (2.6)	16.0	17.8
4–6	1.1 (–)	3.3 (–)	0.1 (0.1)	0.2 (0)	1.3 (1.2)	3.7	3.9
6–8	0	1.7 (–)	0.2 (0)	0.1 (0)	0.6 (0.6)	2.0	7.4

TABLE IV. *Pharmacokinetic parameters after administration of pancuronium, Org 6368 and gallamine in control cats, sham-operated cats (only in the case of Org 6368) and cats with cholestasis. Mean ± SEM. * Significant difference from control*

	Pancuronium		Org 6368			Gallamine	
	Control	Cholestasis	Control	Sham	Cholestasis	Control	Cholestasis
$T_{\frac{1}{2}}{}^{\alpha}$ (min)	4.98 ± 1.37	9.04 ± 5.35	2.46 ± 0.32	1.47 ± 0.14	5.91 ± 1.61*	1.91 ± 0.36	2.26 ± 0.51
$T_{\frac{1}{2}}{}^{\beta}$ (min)	35.60 ± 3.56	70.05 ± 15.08*	13.64 ± 0.97	8.69 ± 1.96	47.46 ± 10.58*	30.6 ± 10.5	30.8 ± 0.9
$T_{\frac{1}{2}}{}^{\gamma}$ (min)						440 ± 99	309 ± 60
Cl (ml min^{-1} kg^{-1})	10.86 ± 1.92	5.89 ± 0.64*	51.30 ± 10.76	78.73 ± 28.14	8.15 ± 3.55*	3.11 ± 0.59	2.58 ± 0.34
V_1 (litre kg^{-1})	0.174 ± 0.042	0.187 ± 0.027	0.263 ± 0.073	0.233 ± 0.063	0.123 ± 0.012	0.097 ± 0.012	0.117 ± 0.020
V^{ss} (litre kg^{-1})	0.373 ± 0.050	0.421 ± 0.028	0.450 ± 0.154	0.460 ± 0.123	0.290 ± 0.027	0.304 ± 0.038	0.289 ± 0.049

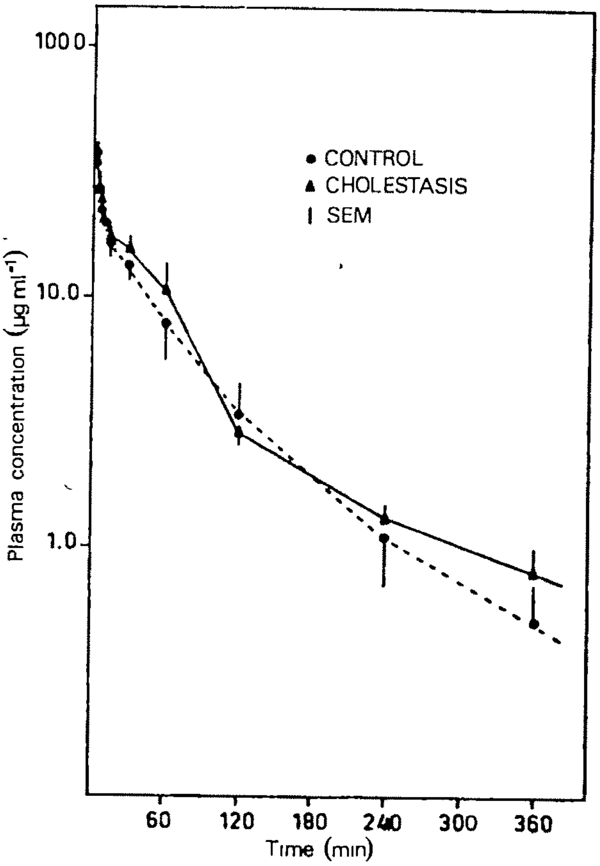

FIG. 8. Semilogarithmic plot of the mean concentration–time profiles of gallamine in control cats ($n = 5$) and cats with cholestasis ($n = 5$).

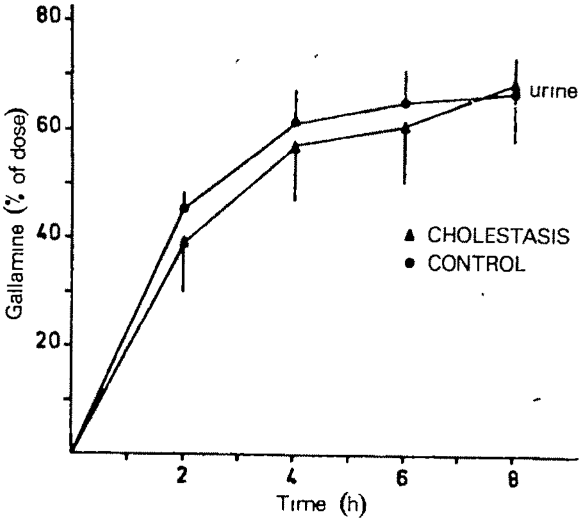

FIG. 9. Cumulative urinary excretion of gallamine in control cats ($n = 5$) and cats with cholestasis ($n = 5$). Mean ± SEM.

(table III). At the end of the observation period, the livers in both groups contained virtually the 3-hydroxy derivative alone. The metabolism of pancuronium to its hydroxy-derivatives showed a pattern comparable to Org 6368 (table III).

The fluorimetric yields of livers after enzymatic pretreatment with β-glucuronidase and aryl-sulphatase did not differ significantly from that of non-enzyme treated livers.

DISCUSSION

The decrease in the plasma clearance and the concomitant prolongation of action of Org 6368 and pancuronium in cats with cholestasis may have several causes.

(a) *A decrease in renal clearance.* The physico-chemical properties of the bis(tris)-quaternary neuromuscular blocking drugs such as their relatively low lipid solubility and moderate protein binding (Meijer and Weitering, 1970; Waser, 1973; Meijer, Weitering and Vonk, 1976; Meijer et al., 1979) explain why renal elimination of such bis(tris)-quaternary drugs occurs by glomerular filtration (Cohen, Brewer and Smith, 1967; Raaflaub and Frey, 1972). However, renal failure as a cause of the marked decrease in the plasma clearance of the muscle relaxants Org 6368 and pancuronium in extrahepatic cholestasis observed in the present study is not very likely since renal function tests indicate a normal glomerular filtration rate. This conclusion is supported by the finding of normal kinetics of gallamine in the cats with cholestasis.

(b) *A decrease in metabolism.* Duvaldestin and colleagues (1978) investigated the fate of pancuronium in patients with liver cirrhosis and reported a decrease in the biotransformation of pancuronium to its 3-deacetylated metabolite. Possibly, plasma cholinesterase plays a role in the breakdown of the acetylated steroid compounds and this enzyme is synthetized by the liver (Kalow, 1959; Schuh, 1977). Biotransformation patterns of Org 6368 and pancuronium in cats with and without cholestasis in the present study were very similar. A similar result was found for pancuronium in man (Somogyi et al., 1977).

(c) *A decrease in biliary excretion.* The marked decrease in biliary output of pancuronium and Org 6368 in extrahepatic cholestasis cannot explain the pharmacological behaviour, since biliary excretion in control animals was small for both compounds. The biliary output of gallamine in extrahepatic cholestasis was not significantly different from control.

(d) *A decrease in hepatic uptake.* Inhibition of this process might explain the decreased plasma clearance of Org 6368 and pancuronium. The following observations point to a decreased hepatic uptake: the significant decrease in the liver content of pancuronium after 8 h in extrahepatic cholestasis, and the marked decrease in liver to plasma partition ratio for Org 6368.

The data and observations presented here support the concept that cholestasis causes an impairment of the hepatic transport at the uptake level. The mechanism of this effect could be an interaction of the steroid neuromuscular blocking drugs with naturally occurring bile components, most likely bile salts. Several authors reported impairment of biotransformation of drugs during extrahepatic cholestasis, caused by increased concentrations of bile salts (McLuen and Fouts, 1961; Hutterer et al., 1970). Vonk and others (1978a, b) observed that bile salts at concentrations of about 100 μmol litre^{-1} and greater inhibit hepatocellular uptake of the organic cations tubocurarine and acetyl-procainamide ethobromide in intact rats, isolated rat livers and isolated hepatocytes. Recently, we have shown a prolongation of the duration of action of Org 6368 by bile salts as a result of inhibition of primary hepatic uptake (Vonk et al., 1979). The present investigations show that the concentrations of bile salt in plasma after 9–10 days cholestasis were increased from the normal value of 2 μmol litre^{-1} to 500 μmol litre^{-1}. According to previous studies these increased concentrations could very well account for the impaired hepatic uptake of the bisquaternary steroidal agents.

There is no simple explanation for the greater total recovery of Org 6368 and pancuronium and their metabolite(s) in extrahepatic cholestasis. Formation of conjugates with sulphuric or glucuronic acid, or both, could be excluded. Similar findings were obtained (Buzello, 1975) for pancuronium in man. It is possible that changes in distribution in hepatic or extrahepatic tissues, or both, occurred.

The present results confirm the study of Somogyi, Shanks and Triggs (1977) that the use of pancuronium and other steroid neuromuscular blocking drugs in the commonly used dosage regime in patients with extrahepatic cholestasis may cause unexpected prolongation of action.

ACKNOWLEDGEMENTS

We wish to thank Prof. Dr D. K. F. Meijer and Prof. Dr H. Wesseling for discussing the manuscript, Dr D. S. Savage (Organon Laboratories Ltd, Newhouse) for the supply of Org 6368 and Mrs U. W. Kersten for her analytical help.

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EFFET D'UNE CHOLESTASE EXPERIMENTALE SUR LES AGENTS DE BLOCAGE NEUROMUSCULAIRE CHEZ LES CHATS

RESUME

On a comparé le pancuronium, Org 6368 et la gallamine sur des chats témoins et sur des chats ayant une cholestase expérimentale. On a constaté sur ces derniers une diminution du coefficient d'épuration plasmatique, ainsi qu'une prolongation du blocage neuromusculaire avec Org 6368 et le pancuronium; alors qu'aucune différence importante n'a été décelée dans le modèle de biotransformation d'Org 6368 et du pancuronium par rapport aux témoins. L'inhibition de la fixation hépatique d'Org 6368 et du pancuronium dans une cholestase extra-hépatique peut expliquer les modifications importantes survenues dans la pharmacocinétique des deux agents de blocage neuromusculaire stéroïdes. La pharmacocinétique de la gallamine a été normale pendant la cholestase. Les résultats laissent penser que dans des conditions pathologiques mettant en cause des concentrations plus fortes de sels biliaries dans le plasma, les agents de blocage neuromusculaire qui sont dégagés du plasma par le foie peuvent avoir une fixation hépatique altérée et donc une durée d'action prolongée.

EFFEKT VON EXPERIMENTELLER CHOLESTASE AUF NEUROMUSKULÄRE BLOCKIERUNGSDROGEN IN KATZEN

ZUSAMMENFASSUNG

Pancuronium, Org 6368 und Gallamin wurden verglichen—in einer Kontrollgruppe von Katzen, und bei Katzen mit experimenteller Cholestase. In letzterer Gruppe wurde eine sinkende Plasmaklärung und eine Verlängerung der neuromuskulären Blockierung bei Org 6368 und Pancuronium festgestellt; der Ablauf der Biotransformation dieser Drogen unterschied sich auch nicht von dem in der Kontrollgruppe. Die Unterdrückung der Leberaufnahme dieser beiden Drogen bei extrahepatischer Cholestase konnte die wesentlichen pharmakokinetischen Veränderungen der beiden Steroiddrogen erklären. Die pharmakokinetischen Vorgänge von Gallamin waren während Cholestase normal. Die Resultate zeigen, dass unter pathologischen Bedingungen—erhohte Plasmakonzentrationen von Gallensalzen—neuromuskulare Blockierungsmittel, die von der Leber aus dem Plasma geklärt werden, nicht so leicht von der Leber aufgenommen werden konnen und daher eine längere Wirkungsdauer haben konnen.

EFECTO DE LAS DROGAS DE BLOQUEO NEUROMUSCULAR EN GATOS CON COLESTASIS EXPERIMENTAL

SUMARIO

Se compararon pancuronium, Org 6368 y gallamina en gatos de control y en gatos con colestasis experimental. En estos últimos se apreció, usando Org 6368 y pancuronium, una disminución en eliminación de plasma y una prolongación del bloqueo neuromuscular. No se detectó diferencia significativa alguna en el modelo de biotrans-

formación del Org 6368 ni en el del pancuronium, en comparación con el de los gatos de control. La inhibición de absorción hepática de Org 6368 y de pancuronium en colestasis extrahepática puede que explique la significativa alteración en las farmacocinéticas de las dos drogas esteroides de bloqueo neuromuscular. Las farmacocinéticas de la gallamina fueron normales durante la colestasis. Los resultados sugieren que, bajo condiciones patológicas en las que acontezcan mayores concentraciones de sales biliares en el plasma, los agentes de bloqueo neuromuscular que el hígado extrae del plasma, pueden sufrir una absorción hepática perjudicial y, por consiguiente, una acción de duración prolongada.

Br. J. Anaesth. (1980), **52**, 759

SCREENING OF CERTAIN ANAESTHETIC AGENTS FOR THEIR ABILITY TO ELICIT ACUTE PORPHYRIC PHASES IN SUSCEPTIBLE PATIENTS

G. H. BLEKKENHORST, G. G. HARRISON, E. S. COOK AND L. EALES

SUMMARY

The activity of δ-aminolaevulinic acid synthetase (E.C. 2.3.1.37) (ALA–S) was measured in rat liver after the simultaneous administration of various anaesthetic agents and 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) *in vivo*. Flunitrazepam, Althesin and phenobarbitone caused a significant increase in the activity of the enzyme which was not observed with propanidid, etomidate and minaxolone. It is suggested that DDC-treated rat, which resembles latent human variegate porphyria, may be a more valid method of testing drugs for their ability to elicit acute porphyric phases in susceptible individuals. The anaesthetic agents which induced the activity of hepatic ALA–S in this model are not recommended in patients with genetic hepatic porphyria.

The porphyrias are a group of disorders of haem metabolism characterized by specific patterns of haem precursor overproduction, accumulation and excretion, each pattern defining a particular form of porphyria. Variegate, or South African genetic porphyria, is one of the forms particularly common in southern Africa. It has been estimated that there are more than 8000 susceptible individuals (Dean, 1971) with a frequency of 1 in 250 in one region. The acute phase of this condition and of two other forms of the hereditary "hepatic" porphyrias, acute intermittent porphyria and hereditary coproporphyria, may be life-threatening. It is usually caused by exposure of the susceptible individual to drugs, particularly barbiturates (Eales, 1971). The frequency of acute porphyric attacks in South Africa has been reduced dramatically by effective family surveys, when asymptomatic but biochemically positive members of families have been warned to avoid precipitating agents (Eales, 1971). Identification of drugs which are porphyrogenic is also necessary to prevent life-threatening acute porphyric crises. Previously this has been largely a process of trial and error or anecdote, but it is now possible to identify the porphyrogenicity of drugs in the laboratory.

Rats given a relatively low dose of 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) exhibit a condition which resembles latent human variegate porphyria. The animals become sensitive to drugs which can precipitate the metabolic disorder such that, biochemically, the reaction is typical of the human attack (De Matteis, 1973). We have used the DDC-primed rat to test the porphyrogenicity of phenobarbitone and the i.v. anaesthetic agents Althesin, etomidate, flunitrazepam, propanidid and minaxolone by determination of the activity of hepatic δ-aminolaevulinic acid synthetase (E.C. 2.3.1.37) (ALA–S). This is the initial and rate-limiting enzyme of haem biosynthesis (Granick and Urata, 1963) and is increased in the three hereditary "hepatic" porphyrias (Elder, Gray and Nicholson, 1972; Meyer and Schmid, 1973).

MATERIALS AND METHODS

Male Wistar rats (weight 180–220 g) were starved for 24 h but water was freely allowed. In each experiment the five animals in the control group each received arachis oil 1 ml; the second group of five received the drug under study; a third group of five received DDC 100 mg kg^{-1} suspended in arachis oil and the fourth group received DDC 100 mg kg^{-1} simultaneously with the drug under study. The drugs were administered i.p. in the doses: phenobarbitone (Gardenal, May and Baker, Port Elizabeth, South Africa) 50 mg kg^{-1}; propanidid (Fabantol, Bayer, Leverkusen, Germany) 100 mg kg^{-1}; etomidate (Ethnor, Halfway House, South Africa) 5 mg kg^{-1}; flunitrazepam (Rohypnol, Roche, Isando, South Africa) 0.5 mg kg^{-1}; Althesin (Glaxo–Allenbury, Wadeville, South Africa) 12 mg kg^{-1} and minaxolone (Glaxo Group Research, Greenford, Middlesex, England)

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0007-0912/80/080759-04 $01.00

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15 mg kg^{-1}. The volume of the drug injected was usually 1 ml and drugs were diluted if necessary in sodium chloride solution (0.15 mmol litre; saline).

After 17 h, the animals were sacrificed by decapitation, exsanguinated and the livers removed, blotted free of blood and washed with ice-cold saline. For measurement of ALA–S, the liver was weighed, chopped into small pieces, washed twice with ice-cold saline and homogenized in Tris : HCl buffer 0.01 mol $litre^{-1}$, pH 7.4 containing sodium chloride 0.15 mmol $litre^{-1}$ and EDTA 0.5 mmol $litre^{-1}$ using a motor-driven Teflon pestle in a glass mortar to give a 10% (w/v) homogenate. The assays for ALA–S were performed as described previously (Pimstone, Blekkenhorst and Eales, 1973) using a modification of the method of Strand and others (1972b).

The significance of difference between mean values was assessed by Student's *t* test.

RESULTS

A preliminary experiment established that a dose of DDC 100 mg kg^{-1} gave a maximal increase in ALA–S activity when administered with phenobarbitone, a known porphyrogen (Eales, 1971). When administered alone, this dose of DDC gave only a modest increase in ALA–S activity.

The activity of hepatic ALA–S in rats treated with the anaesthetic agents together with DDC is shown in figure 1. Phenobarbitone and DDC caused an increase in the activity of the enzyme but no change was observed in the activity when propanidid and DDC were administered compared with the activity of ALA–S when DDC alone was given. No significant difference in hepatic ALA–S activity was observed when etomidate and minaxolone were given together with DDC, but flunitrazepam and Althesin given with DDC caused an increase in the activity of hepatic ALA–S ($P < 0.05$).

The activities of the enzyme in rats treated with only the drug under test were in all cases found to be not significantly different from those in rats receiving oil only.

DISCUSSION

The results of this study demonstrate that phenobarbitone and the anaesthetic agents flunitrazepam and Althesin, when given simultaneously with DDC to rats cause a significant increase in the activity of hepatic ALA–S compared with the activity of the enzyme when DDC is given alone. On this basis, these drugs must be regarded as porphyrogenic and contraindicated in patients with genetic porphyria.

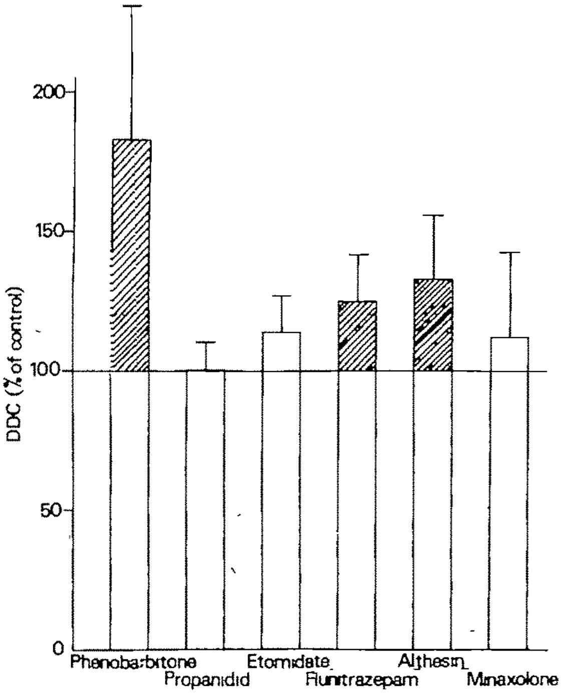

FIG. 1. Hepatic δ-aminolaevulinic acid synthetase (ALA–S) activity in male rats treated simultaneously with 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) and various drugs. Each result represents the mean for five animals; bars indicate SD. One hundred per cent of DDC control= ALA 479 ± SD 58 ($n = 10$) nmol formed per hour per gram of liver. Hatched bars indicate a significant difference ($P < 0.05$) when compared with DDC controls.

A similar investigation (Parikh and Moore, 1978) showed that repeated doses of various anaesthetic agents, including Althesin and etomidate, increased hepatic ALA–S activity. The experimental approach adopted by these workers may not be correct to screen drugs for their porphyrogenicity, since it appears that increased activity of hepatic ALA–S results from the coexistence of two requirements, each of which alone may have little or no effect on the enzyme. These are: first, an effect on haem synthesis and, second, exposure to lipid-soluble inducers of haemoprotein synthesis (Maxwell and Meyer, 1978). Thus when rats are primed with small doses of DDC which cause a partial block at the ferrochelatase level (De Matteis, 1973), and a lipid-soluble inducer of haemoprotein synthesis such as phenobarbitone is administered, a potentiation of ALA–S activity is observed. However, single doses of the inducing drugs administered to animals with an intact haem biosynthetic pathway have little effect on hepatic ALA–S activity (De Matteis, 1978; Maxwell and Meyer, 1978).

Similarly, inducing drugs can superimpose their effects on ALA–S in the hereditary hepatic porphyrias. The basis genetic defects in the haem biosynthetic pathway have been shown to be decreased uroporphyrinogen synthetase in acute intermittent porphyria (Strand et al., 1972a), decreased coproporphyrinogen oxidase in hereditary coproporphyria (Elder et al., 1977) and a decreased ferrochelatase activity (Becker et al., 1977) and decreased protoporphyrinogen oxidase, or both (Brenner and Bloomer, 1979), in variegate porphyria. When these drugs are administered to patients with the metabolic defect, the acute porphyric phase becomes manifest, with an inappropriate increase in hepatic ALA–S activity (Meyer and Schmid, 1973).

The determination of hepatic ALA–S in the DDC-primed rat, which biochemically resembles latent variegate porphyria, appears to be a reliable technique in screening drugs for their potential porphyrogenicity. Phenobarbitone is the classic porphyrogenic agent, while propanidid is known from clinical use to be free of this disadvantage. The inclusion of these drugs among those tested serves to an extent as a control of the method. This method appears more sensitive than determination of hepatic haem precursors after administration of DDC and drugs (Eales and Blekkenhorst, 1978), when large variations in the individual responses of rats to the drugs were observed. It should be pointed out, however, that induction of ALA–S by drugs is a dose-related phenomenon, and a large species variation in the therapeutic or toxic effects of chemical substances exists. Furthermore, there is an interspecies variation in drug metabolism and pharmacological response especially to liposoluble drugs (Brodie and Reid, 1971), all of which must be considered when extrapolating these findings to man. In the present experiments, large doses were used, but less than the known lethal doses of the anaesthetic agents. The *in vivo* screening technique presented here is more valid than the exquisitely sensitive chick embryo liver cell culture (Granick, 1966) and chick embryo *in vivo* (Anderson, 1978) screening systems, in which metabolites which may augment synthesis of ALA–S cannot be readily excreted. It is conceivable that some drugs classed as porphyrogenic using these methods might be safe to use in the hereditary hepatic porphyrias.

In this investigation of the porphyrogenicity of newer i.v. anaesthetic agents, we conclude that etomidate and minaxolone are probably non-porphyrogenic in susceptible patients, whereas Althesin and flunitrazepam are likely to be dangerous. Nevertheless, the ultimate test of porphyrogenicity of these anaesthetics can only be the response of individuals who suffer genetic porphyria to administration of these agents.

ACKNOWLEDGEMENT

We thank the South African Medical Research Council for financial support.

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DEPISTAGE DE CERTAINS AGENTS ANESTHESIANTS SUSCEPTIBLES DE PROVOQUER DES PHASES PORPHYRIQUES AIGUES SUR DES MALADES SUJETS A CE GENRE DE REACTION

RESUME

On a mesuré l'activité de l'acide δ-aminolévulinique synthétase (E.C. 2.3.1.37) (ALA-S) dans le foie d'un rat après l'administration simultanée de divers agents anesthésiants et de 3,5-diéthoxycarbonyle-1,4-dihydrocollidine (DDC) *in vivo*. Le flunitrazépam, l'Althésine et le phénobarbitone ont provoqué une augmentation significative de l'activité de l'enzyme, ce que l'on n'a pas observé avec le propanidide, l'étomidate et le minaxolone. Ceci laisse penser que le rat traité au DDC, lequel ressemble à la porphyrie humaine diversicolore latente, peut constituer une méthode plus valable d'essayer les médicaments susceptibles de provoquer des phases porphyriques aigues sur les individus sujets à ce type de réaction. Les agents anesthésiants qui ont provoqué l'activité de l'ALA-S hépatique dans ce modèle ne sont pas recommandés pour les malades souffrant de porphyrie hépatique génétique.

PRÜFUNG GEWISSER NARKOSEMITTEL AUF IHRE EIGENSCHAFT, AKUTE PORPHYRIEPHASEN IN ANFÄLLIGEN PATIENTEN HERVORZURUFEN

ZUSAMMENFASSUNG

Die Aktivität von δ-aminolävulinische Säure-Synthetase (E.C. 2.3.1.37) (ALA-S) wurde in der Rattenleber gemessen nach gleichzeitiger Verabreichung verschiedener Narkosemittel und von 3,5-Diethoxycarbonyl-1,4-dihydrocollidin (DDC) *in vivo*. Flunitrazepam, Althesin und Phenobarbiton bewirkten einen wesentlichen Aktivitätsanstieg des Enzyms, der bei Propanidid, Etomidat und Minaxolon nicht beobachtet wurde. Man nimmt an, dass eine mit DDC behandelte Ratte, die eine menschenähnliche Porphyrie aufweist, eine gültigere Methode zur Überprüfung von Drogen auf ihre Eigenschaft hin darstellt, akute Porphyriephasen bei anfälligen Individuen hervorzurufen. Die Narkosemittel, die in diesem Modell die Aktivitat von hepatischer ALA-S hervorriefen, werden fur Patienten mit genetischer hepatischer Porphyrie nicht empfohlen.

SELECCION DE CIERTOS AGENTES ANESTESICOS CON ARREGLO A SU HABILIDAD PARA ELUCIDAR LAS FASES PORFIRICAS EN PACIENTES SUSCEPTIBLES

SUMARIO

Se midió la actividad de la sintetasa de acido δ-aminolevulínico (E.C. 2.3.1.37) (ALA-S) en el hígado de rata, después de la administración simultánea de varios agentes anestésicos y de 3,5-dietoxicarbonil-1,4-dihidrocollidina (DDC) *in vivo*. El flunitrazepam, la Altesina y la fenobarbitona ocasionaron un incremento significativo en la actividad de la enzima, que no se observó con la propanidida, etomidate ni con la minaxolona. Parece ser que el tratamiento de la rata con DDC, que se asemeja a la variedad de porfiria latente en el ser humano, es un método de mayor validez para la verificación de drogas respecto a su habilidad para elucidar las fases porfíricas agudas en individuos susceptibles. Los agentes anestésicos que indujeron la actividad del ALA-S hepático en este modelo, no se recomiendan para pacientes con porfiria hepática de tipo genético.

Br. J. Anaesth. (1980) **52**, 763

PULMONARY ARTERIOVENOUS SHUNTS DURING HALOTHANE ANAESTHESIA IN DOGS*

D. J. PAVLIN, J. FERENS, D. R. ALLEN AND F. W. CHENEY

SUMMARY

The fraction of cardiac output flowing through pulmonary arteriovenous anastomoses ($\dot{Q}_{av}/\dot{Q}_t$) was measured in dogs during halothane anaesthesia and compared with results obtained in normal awake dogs. Flow through arteriovenous anastomoses was measured using ^{99m}Tc-labelled polystyrene microspheres (50 μm diameter). The fraction of cardiac output perfusing pulmonary arteriovenous anastomoses during halothane anaesthesia was 4.1% (±SD 1.75) compared with 4.6% (±SD 0.73) in air-breathing awake control dogs. In spite of variations in arteriovenous shunt fraction, no significant relationship between the $\dot{Q}_{av}/\dot{Q}_t$ and $\dot{Q}_s/\dot{Q}_t$ was detected. These results suggest that pulmonary arteriovenous anastomoses do not contribute significantly to the physiological shunt observed during halothane anaesthesia.

General anaesthesia is frequently associated with an increase in the alveolar–arterial oxygen tension gradient ($P\mathrm{A}_{O_2}-P\mathrm{A}_{O_2}$) and physiological shunt fraction ($\dot{Q}_s/\dot{Q}_t$ with $F\mathrm{I}_{O_2}$ 1.0) (Campbell, Nunn and Peckett, 1958; Stark and Smith, 1960; Theye and Tuohy, 1964; Panday and Nunn, 1968; Marshall, Cohen and Klingenmaier, 1969; Stone et al., 1975). The intrapulmonary component of physiological shunt may result from blood perfusing non-ventilated alveoli or blood passing through direct arteriovenous (A–V) anastomoses. The size, distribution and physiological role of A–V anastomoses is poorly understood, and their contribution to the total physiological shunt fraction during general anaesthesia unknown. Although often suggested as a potential cause of hypoxia during anaesthesia (Marshall and Wyche, 1972; Rehder, Sessler and Marsh, 1975), flow through these channels has not been measured during general anaesthesia and compared with the awake control state.

It has been suggested that these channels may open in response to increased pulmonary artery pressure (Cheney et al., 1978), beta-adrenergic stimulation or general anaesthesia. Balchum and others (1968) by direct observation during angiography, reported opening of such channels when pulmonary artery pressure was increased. More recently, measurements of A–V shunt flow have been made using radioactively labelled microspheres. Using such quantitative methods, increasing pulmonary artery pressure was found to have no effect on A–V shunt flow (Cheney et al., 1978). Nomoto and others (1974) used similar techniques and reported a five-fold increase in anastomotic shunt flow in dogs during adrenaline infusion, which led them to suggest that these channels may open in response to beta-adrenergic stimulation.

The purpose of this study was to assess the role of A–V anastomoses as a cause of hypoxia during halothane anaesthesia since halothane might open the channels either directly by causing relaxation of vascular smooth muscle or indirectly by a beta-agonist effect (Price et al., 1970). Such a mechanism might partially explain the decrease in $P\mathrm{a}_{O_2}$ commonly observed during anaesthesia with halothane and other inhalation agents. The method was designed to measure the fraction of cardiac output shunted through pulmonary A–V channels during halothane anaesthesia compared with the awake control state.

METHODS

Group 1. *Halothane anaesthesia*

Anaesthesia was induced with halothane in nine adult unpremedicated male mongrel dogs, weighing 8–38 kg. Each animal was placed supine, the trachea was intubated with a cuffed tube, and anaesthesia was maintained with 1% halothane in oxygen. Ventilation was controlled using a Harvard pump to deliver a tidal volume of 15 ml kg^{-1}, and the respiratory frequency adjusted to maintain $P\mathrm{a}_{CO_2}$ between

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* Presented at the American Society of Anesthesiologists Annual Meeting, Chicago, Illinois, 1975.

0007-0912/80/080763-06 $01.00

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3.7 and 5.3 kPa. Catheters were introduced to the femoral artery, inferior vena cava (IVC), pulmonary artery (PA) and the left ventricle (LV) via the carotid artery. A sodium iodide detector was positioned over the head of the animal and a lead shield placed over the shoulders so that placement of a radioactive sample on the chest resulted in no increase in background counts recorded over the head.

The details of the radioactive microsphere technique for measuring A–V anastomotic shunt fraction have been reported previously (Cheney et al., 1978). Microspheres (43–53 μm diameter) labelled with technetium-99m were injected into the left ventricle and the count rate over the head of the dog measured for 5 min using a Picker dual probe sodium iodide detector with a single channel analyser and scaler. A second injection of microspheres was then made into IVC and activity determined over a subsequent 5-min period. A–V anastomotic shunt fraction was calculated as described below. Measurements of pulmonary and systemic vascular pressures, cardiac output, arterial and mixed venous blood-gas tensions, haemoglobin concentration and percent saturation were made in the same time period following each injection of microspheres.

Physiological shunt fraction ($\dot{Q}_s/\dot{Q}_t$ when $F\text{I}_{O_2} = 1.0$) was determined by the oxygen technique using the standard shunt equation. Cardiac output was measured by the dye dilution technique using indocyanine green. Blood-gas tensions were measured with a Radiometer blood-gas analyser.

Arteriovenous shunt calculation. A–V shunt was determined by plotting activity in accumulated counts per 30 s against time and extrapolating the data to obtain the count rate 30 s after LV and IVC injections (fig. 1). This interval was chosen arbitrarily to allow time for complete circulation of blood and microspheres from the injection site at IVC to the point of lodging in the head. The total amount of activity injected was determined by measurement before injection (range 50–750 μCi).

The anastomotic shunt ($\dot{Q}_{av}/\dot{Q}_t$) was calculated as follows (method 1):

$$\frac{\dot{Q}_{av}}{\dot{Q}_t} = \frac{\text{increased count rate after IVC injection}}{\text{increased count rate after LV injection}} \times \frac{A_{LV}}{A_{IVC}}$$

where A_{LV} and A_{IVC} are the activity of ^{99m}Tc-labelled spheres injected into the LV and IVC respectively. All count rates were corrected for background activity and decay of technetium-99m.

Group 2. Awake control

The technique described above required the animal to remain motionless during the counting period and was therefore inappropriate for measurement of A–V shunt in the awake state. Therefore, a modification was used to measure $\dot{Q}_{av}$ in five awake animals (group 2).

Radioactive microspheres injected i.v. will either pass through A–V shunts in the lung and lodge in the microcirculation of the remainder of the body (carcass) or will be trapped in the microcirculation of the lung. A catheter was inserted to a peripheral vein in the forelimb of an awake dog and labelled microspheres injected followed immediately by 10 ml of isotonic saline. The animal was sacrificed after 2 min by injection of sodium thiopentone 2 g i.v. The chest was opened immediately and clamps placed across the pulmonary arteries and veins at the hilum. The pulmonary vessels were severed between clamps so that no blood was allowed to escape from either the proximal or distal ends of the cut vessels. The lungs were then removed and placed in a plastic bag. The radioactivity in the lungs and in the remainder of the body was determined separately using a gamma counter. The A–V shunt fraction was determined as follows (method 2):

$$\frac{\text{(counts in carcass)}}{\text{(counts in carcass} + \text{lungs)}} = \frac{\dot{Q}_{av}}{\dot{Q}_t} = \text{arteriovenous shunt fraction}$$

It was possible that sacrificing the animal might have affected the distribution of microspheres between the lung and the remainder of the body. Three experiments were performed to determine the effects of sacrificing an animal by injection of sodium thiopentone 2 g i.v. In three dogs anaesthetized with halothane, an injection of labelled microspheres was made to the IVC and baseline counts over the head recorded for 5 min. Sodium thiopentone 2 g was then injected i.v. No change in the amount of activity counted over the head was detected after 3 min ($P < 0.05$; Student's t test for non-paired data). It was concluded that this method of sacrificing awake control dogs did not dislodge microspheres trapped previously in the lungs.

Group 3. Halothane anaesthetized dogs

A–V shunt fraction was measured by method 2 in an additional group of four animals anaesthetized with 1% halothane in 99% oxygen. To determine

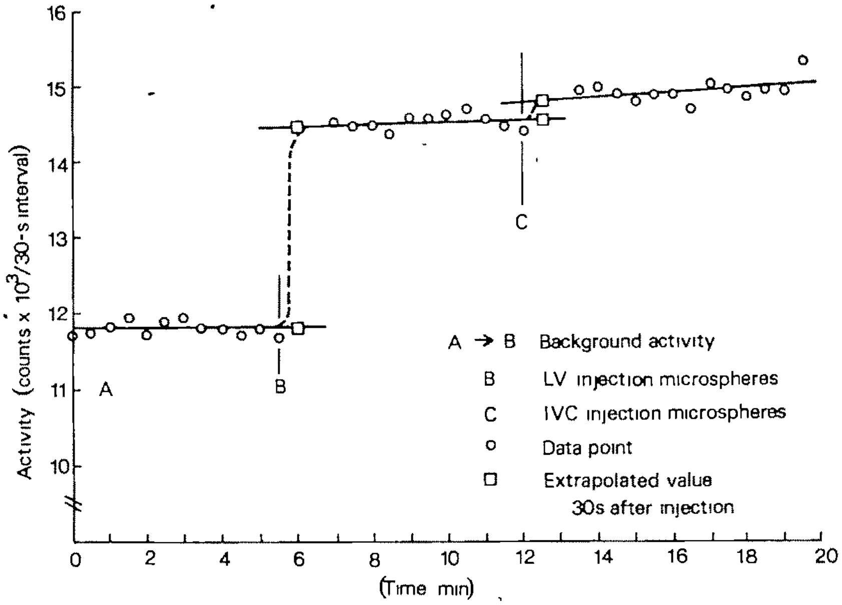

FIG. 1. Typical arteriovenous shunt determination in a dog during halothane anaesthesia using ^{99m}Tc-labelled microspheres; A→B = background radioactivity, B = left ventricular injection of microspheres, C = inferior vena cava injection of microspheres; ○ = radioactive counts $\times 10^3$/30-s interval; □ = extrapolated counts 30 s after microsphere injection.

whether the two different methods of measuring A–V shunt flow produced comparable results. Anaesthesia was induced by inhalation of 4% halothane in oxygen by mask and maintained by spontaneous ventilation with 1% halothane in oxygen. Labelled microspheres (43–53 μm diameter) were injected i.v. to a forepaw vein, and flushed with 5 ml of saline. After 2 min, the animal was sacrificed by injection of sodium thiopentone 2 g. Thoracotomy was performed rapidly, proximal and distal clamps placed across both hila and the lungs removed by severing between the clamps. Radioactivity in the remaining carcass and in the lungs was determined separately using a gamma counter. The A–V shunt fraction was then calculated as described previously in the normal awake control group (method 2).

RESULTS

Halothane anaesthesia caused no significant change in the fraction of cardiac output perfusing A-V shunts compared with the awake control state (fig. 2). Mean $\dot{Q}_{av}/\dot{Q}_t$ measured during halothane anaesthesia (group 1) was 4.1% (± SD 1.75) using method 1, compared with 4.6% (± SD 0.73) in the awake control dogs (group 2) using method 2. When Pa_{O_2} and physiological shunt were compared (using correlation

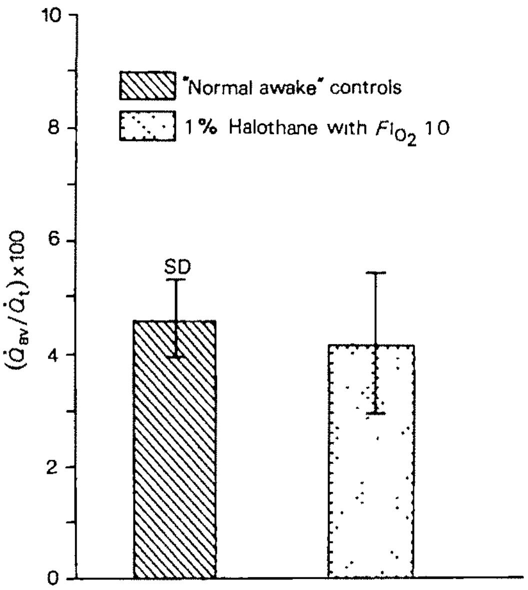

FIG. 2. Arteriovenous shunt flow expressed as a percentage of cardiac output in normal awake control dogs (group 2, cross-hatched bars), and during 1% halothane anaesthesia (group 1, stippled bars).

TABLE I. *Physiological and arteriovenous shunt and cardiovascular results during halothane anaesthesia. MAP= mean arterial pressure, CI= cardiac index,* $P\overline{\mathrm{AW}}$*= mean pulmonary artery wedge pressure,* $P\overline{\mathrm{AP}}$*= mean pulmonary artery pressure, PVR= pulmonary vascular resistance; r= correlation coefficient between* $\dot{Q}_{av}/\dot{Q}_t$ *and haemodynamic variables; n.s.= no significant correlation* ($P > 0.05$).

	$\dot{Q}_{av}/\dot{Q}_t$ ×100	$\dot{Q}_s/\dot{Q}_t$ ×100	MAP (kPa)	CI (litre min^{-1} m^{-2})	$P\overline{\mathrm{AW}}$ (kPa)	$P\overline{\mathrm{AP}}$ (kPa)	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	PVR (kPa $litre^{-1}$ min)
	1.3	10.5	14.2	2.86	0	1.3	69	4.5	0.47
	2.7	10.5	11.6	1.04	1.3	2.5	74	4.1	1.22
	3.0	12.0	14.1	1.94	0	2.1	62	4.0	1.10
	3.3	11.5	12.8	1.42	1.3	1.2	72	4.3	0.85
	4.3	11.0	12.6	4.03	0.4	2.0	68	4.6	0.50
	4.5	10.5	15.3	2.09	0.9	2.4	66	4.6	0.71
	4.8	10.0	14.9	3.60	0.7	2.2	66	7.4	0.43
	6.2	11.0	15.5	2.07	0.5	1.8	68	7.4	0.74
	6.9	11.5	15.8	1.45	0.5	2.0	68	4.0	1.49
Mean	4.1	11.2	14.1	2.28	0.6	2.0	68	4.2	0.83
SD	1.8	0.9	1.5	1.02	0.46	0.4	3.5	0.4	0.37
r		±0.46	±0.62	−0.02	−0.02	+0.26	0	−0.45	0
Significance		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

analysis) with simultaneously determined $\dot{Q}_{av}/\dot{Q}_t$ in group 1, no significant relationship was detected. Similar analysis of data failed to reveal any significant relationship between anastomotic shunt fraction and mean pulmonary artery pressure, mean pulmonary artery wedge pressure, pulmonary vascular resistance or cardiac index, suggesting that none of these variables has any direct influence on $\dot{Q}_{av}/\dot{Q}_t$ (table I). The mean value of $\dot{Q}_{av}/\dot{Q}_t$ during halothane anaesthesia measured using method 2 in group 3 was 2.3% (±SD 0.23). This was not significantly different (Student's *t* test for unpaired data) from the values obtained in group 1 animals using method 1 ($P > 0.05$) indicating that the two methods of determining the A–V shunt fraction produce comparable results.

DISCUSSION

The validity of the radioactive microsphere technique for measuring regional distribution of blood flow has been demonstrated previously (Rudolph and Heymann, 1967; Wagner et al., 1969). Using similar techniques, Strauss and others (1969) and Nomoto and colleagues (1974) found 2.2 and 2.1% anastomotic shunt respectively in dogs anaesthetized with pentobarbitone. These figures are slightly less than those obtained in this study and this may be explained by small differences in composition or size of microspheres used in different laboratories.

Under conditions similar to those in which halothane is administered clinically, there was no significant change in the fraction of cardiac output flowing through A–V anastomoses compared with awake control values. Conclusions are based on the measurement of A–V shunt fraction with a single size microsphere (43–53 μm diameter). Spheres of this size were chosen to avoid measurement of blood flow through capillaries which are considered to be 5–15 μm in diameter (Weibel, 1963). Although flow through shunts with a diameter of less than 50 μm will not be measured by this technique, it is likely that microspheres will be squeezed through normal capillaries when smaller microspheres are chosen as indicators. We have shown previously that values of shunt determined using larger microspheres (110 μm) are near zero (Cheney et al., 1978). It seems likely, therefore, that the 50-μm spheres provide an adequate assessment of the response of anastomotic channels to anaesthesia and to variation in haemodynamic variables.

The relevance of our results to man is unknown. However, Strauss and others (1969) have found similar values of A–V shunt in man and dog. It therefore seems likely that shunts behave similarly in the two species during anaesthesia. Halothane was chosen for these experiments because of its frequent use in clinical practice and because of its proposed beta-agonist activity. Other volatile agents such as fluoroxene, ether or cyclopropane, which are known to be associated with increased concentrations of catecholamines, might give different results if A–V communications are influenced by catecholamines as proposed by Berk and his colleagues (1967).

In this and in a previous study we have shown that there is no significant relationship between pulmonary artery pressure and arteriovenous shunt flow which suggests that A–V communications do not open in response to increased pulmonary artery pressure.

Despite variation in $\dot{Q}_{av}/\dot{Q}_t$, there was no correlation with $\dot{Q}_s/\dot{Q}_t$, which suggests that A–V anastomotic shunt flow is not a significant factor in $\dot{Q}_s/\dot{Q}_t$ during halothane anaesthesia. It is likely that physiological shunt observed during halothane anaesthesia is a result of shunting of blood through non-ventilated, collapsed areas of lung.

ACKNOWLEDGEMENTS

The authors wish to thank Rodney Gronka and Ed Chappelle for their technical assistance.

This study was supported in part by USPHS Grants GM15991–07 (Anesthesia Research Center) and GM01160–12 (Anesthesia Research Training).

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DERIVATIONS ARTERIOVEINEUSES PULMONAIRES PENDANT UNE ANESTHESIE A L'HALOTHANE SUR DES CHIENS

RESUME

On a mesuré sur des chiens anesthésiés à l'halothane la fraction de débit cardiaque passant à travers des anastomoses artérioveineuses pulmonaires ($\dot{Q}_{av}/\dot{Q}_t$) et on a comparé les résultats obtenus avec ceux de chiens normaux éveillés. On a mesuré le débit passant à travers les anastomoses artérioveineuses à l'aide de microsphères en polystyrène (50 μm de diamètre) marquées ^{99m}Tc. La fraction de débit cardiaque passant au travers des anastomoses artérioveineuses pulmonaires pendant l'anesthésie à l'halothane a été de 4,1% (± écart type 1,75) par rapport à 4,6% (± écart type 0,73) chez les chiens témoins éveillés respirant de l'air. En dépit des variations dans la fraction de dérivation artérioveineuse, on n'a décelé aucune relation notoire entre $\dot{Q}_{av}/\dot{Q}_t$ et $\dot{Q}_s/\dot{Q}_t$. Ces résultats laissent penser que les anastomoses artérioveineuses pulmonaires ne contribuent pas d'une manière significative à la dérivation physiologique observée pendant l'anesthésie à l'halothane.

ARTERIOVENÖSE LUNGEN-SHUNTS BEI HALOTHAN-NARKOSE IN HUNDEN

ZUSAMMENFASSUNG

Der Bruchteil des Herzminutenvolumens, der durch arteriovenose Lungen-Anastomosen fliesst ($\dot{Q}_{av}/\dot{Q}_t$), wurde bei Hunden wahrend einer Halothannarkose gemessen und mit Resultaten bei normal wachen Hunden verglichen. Der Durchfluss durch arteriovenöse Anastomosen wurde mittels ^{99m}Tc-Polystyren-Zentrosomen (50 μm Durchmesser) gemessen. Der Teil des Herzminutenvolumens in den arteriovenosen Lungen-Anastomosen während der Halothannarkose betrug 4,1% (±SD 1,75), verglichen mit 4,6% (±SD 0,73) bei luftatmenden wachen Hunden. Trotz der Anderungen im arteriovenosen Shunt-Anteil wurde keine signifikante Beziehung zwischen $\dot{Q}_{av}/\dot{Q}_t$ und $\dot{Q}_s/\dot{Q}_t$ entdeckt. Die Resultate zeigen, dass arteriovenose Lungen-Anastomosen nicht wesentlich zum physiologischen Shunt beitragen, der während der Halothannarkose beobachtet wurde.

DERIVACIONES ARTERIOVENOSAS DEL PULMON DE PERROS DURANTE ANESTESIA CON HALOTANO

SUMARIO

Se midió en perros la fracción del flujo cardiaco que fluye a través de la anastomosis arteriovenosa de pulmón ($\dot{Q}_{av}/\dot{Q}_t$), durante la anestesia con halotano y se comparó con los resultados obtenidos en perros despiertos y normales. El flujo a través de la anastomosis arteriovenosa se midió usando microesferas de poliestireno irradiadas (^{99m}Tc) (de 50 μm de diámetro). La fracción del flujo cardiaco que filtró la anastomosis arteriovenosa de pulmón durante la anestesia con halotano fue del 4,1% (± desviación típica de 1,75) en comparación con un valor de 4,6% (± desviación típica de 0,73) en perros despiertos de control que respiraban aire. A pesar de las variaciones en la fracción correspondiente a la derivación arteriovenosa, no se detectó relación significativa alguna entre el $\dot{Q}_{av}/\dot{Q}_t$ y el $\dot{Q}_s/\dot{Q}_t$ Estos resultados sugieren que la anastomosis arteriovenosa de pulmón no contribuye de forma significativa a la derivación fisiológica observada durante la anestesia con halotano.

Br. J. Anaesth. (1980), **52**, 769

DIRECT EFFECTS OF TRIMETAPHAN ON THE DOG MESENTERIC ARTERY AND SAPHENOUS VEIN

J. CASTRO-TAVARES

SUMMARY

Direct vascular effects of trimetaphan camsylate were studied in the dog mesenteric artery and lateral saphenous vein; vascular strips were suspended in normal Krebs–Henseleit solution and contraction produced by phenylephrine 2.4 × 10^{-6} mol $litre^{-1}$. Both vessels were relaxed by trimetaphan, maximal relaxation being obtained at the concentration of 1.3 × 10^{-3} mol $litre^{-1}$; this effect was more marked in the vein strips. Calculated ED_{50} for the relaxing effect of trimetaphan was not significantly different between artery and the vein. It is concluded that the sensitivity of arteries and veins to trimetaphan is similar, but that this effect cannot play a significant role in the production of controlled hypotension.

Trimetaphan is a ganglion blocking drug widely used for the induction and maintenance of controlled hypotension during anaesthesia. Apart from its ganglion blocking effect, two other mechanisms are recognized in trimetaphan-induced hypotension (Adams, 1975): a direct effect on vascular smooth muscle and an indirect, histamine-mediated, effect.

Like other drugs used in the induction of controlled hypotension, trimetaphan decreases arterial resistance (Wang, Lin and Katz, 1977) and reduces venous tone (Bhatia and Frohlich, 1973). Different sensitivities of these two types of vessels have been reported, and the results obtained in the intact animal (Wang, Lin and Katz, 1977) suggest that the action of trimetaphan on the arterial bed predominates.

The direct effect of trimetaphan on the vascular smooth muscle and the relative sensitivity of both types of vessel to this depressant effect were studied using isolated strips of the dog mesenteric artery and lateral saphenous vein.

METHODS

Mongrel dogs of both sexes, weight 8–14 kg, were anaesthetized with pentobarbitone 30 mg kg^{-1} i.v. Segments from both lateral saphenous veins and some fine branches of the mesenteric artery were removed and immersed in cold oxygenated Krebs–Henseleit solution. After complete removal of perivascular tissues, the vessels were cut helically (Furchgott and Bhadrakom, 1953). Strips of about 2.4 cm were suspended in a 25-ml bath containing Krebs–Henseleit solution. The bath solution was kept at 37 °C and bubbled with a mixture of 5% carbon dioxide in oxygen. Isotonic contractions were recorded with a resting tension of 1.0 g applied to the arterial and 1.5 g applied to the venous strips.

After an equilibrium period of about 60 min, the strips were contracted with phenylephrine hydrochloride 1.96 × 10^{-6} mol $litre^{-1}$. This concentration is known to evoke a 65–85% maximal contraction (Guimarães, 1975). Trimetaphan-induced relaxation was studied by addition of the drug to the bath containing the phenylephrine contracted preparation.

The Krebs–Henseleit solution, pH 7.4, had the following composition (g $litre^{-1}$): NaCl 9.94; KCl 0.35; $CaCl_2$ 0.28; KH_2PO_4 0.16; $7(H_2O)MgSO_4$ 0.14; $NaHCO_3$ 2.10; glucose 2.15. Trimetaphan camsylate (Arfonad, Roche) was dissolved in deionized water and added cumulatively to the bath, the total volume never exceeding 1.0 ml. The initial concentration of trimetaphan in the bath was 4.2 × 10^{-7} mol $litre^{-1}$, and the cumulative dose–response curve was obtained by adding further doses of trimetaphan. Each addition corresponded to a five-fold increase in drug concentration.

Reported data were obtained from 10 strips collected from at least four dogs and the results are presented as mean ± SEM. Student's *t* test for comparison of un-paired means was used in the statistical analysis.

RESULTS

The relative magnitude of the phenylephrine-evoked contraction was checked at the end of each

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0007-0912/80/080769-03 $01.00

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experiment. When it did not reach 65–80% of the maximal response, the results were discarded.

The maximum relaxing effect of trimetaphan on the mesenteric artery strips (87.3 ± 2.1%) was obtained at the concentration of 1.3×10^{-3} mol litre^{-1} (fig. 1), and was never complete. For the same concentration of trimetaphan, the relaxation of the saphenous vein was also maximal (92.2 ± 3.2%). The difference between these two maximal relaxation values is statistically significant ($P < 0.02$). About half of the isolated saphenous vein strips exhibited a complete relaxation with that concentration of trimetaphan.

The relaxations evoked by trimetaphan 5.2×10^{-5} mol litre^{-1} and 2.6×10^{-4} mol litre^{-1}, on the phenylephrine-contracted arterial strips were significantly different ($P < 0.05$ and $P < 0.01$, respectively) from those recorded in the saphenous veins by the same concentration (fig. 1). The effects evoked in both vessels with lower concentrations were not significantly different.

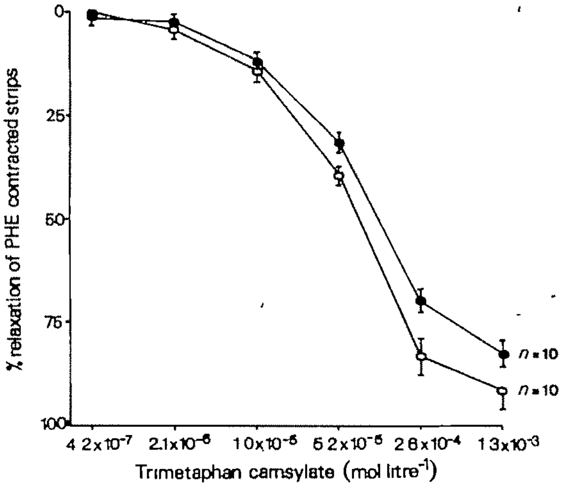

FIG. 1. Trimetaphan-induced relaxation of the isolated dog mesenteric artery (open circles) and saphenous vein (closed circles), previously contracted by phenylephrine hydrochloride; mean ± SEM.

ED_{50} (concentration of trimetaphan camsylate that reduces phenylephrine-induced contraction by 50%), was $1.05 \pm 0.09 \times 10^{-4}$ mol litre^{-1} in the mesenteric artery and $8.46 \pm 0.82 \times 10^{-5}$ mol litre^{-1} in the saphenous vein. These values were not significantly different.

DISCUSSION

Trimetaphan has a depressant effect on vascular strips, which must be attributed to an action on smooth muscle, since there are no intramural sympathetic ganglia in the vessels. The maximal relaxation of the phenylephrine-contracted saphenous vein is significantly greater than the maximal relaxation recorded under the same conditions in the isolated mesenteric arteries. ED_{50}, which is a more accurate index for comparison of sensitivities, yielded no difference between the arterial and venous strips. Thus no difference in the sensitivity of the mesenteric artery and the saphenous vein of the dog to the relaxing direct effect of trimetaphan could be found, in contrast to what is generally reported for the whole animal (Bhatia and Frohlich, 1973).

No information on serum trimetaphan concentrations achieved during induced hypotension is available but we calculate that the concentration may be of the order 0.5–1 μg ml^{-1}, assuming that trimetaphan molecules are not excreted or metabolized and are distributed in all the extracellular water. Our ED_{50} exceeds this value by about one hundred times so that the direct effects of trimetaphan only become apparent at high concentrations which are probably not reached during the induction of controlled hypotension. In the same experimental conditions, arterial and venous smooth muscle are much more sensitive to sodium nitroprusside, confirming its predominant direct action on vascular smooth muscle (Castro-Tavares, 1980).

We conclude that the direct effect of trimetaphan camsylate on the vascular smooth muscle is not clinically significant in the production of controlled hypotension.

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EFFETS DIRECTS DU TRIMETAPHAN SUR L'ARTERE MESENTERIQUE ET LA VEINE SAPHENE DU CHIEN

RESUME

On a étudié les effets directs du camsylate de trimétaphan sur l'artère mésentérique et sur la veine saphène latérale du chien; des bandes vasculaires ont été suspendues dans une solution normale de Krebs–Henseleit et la contraction a été produite par de la phényléphrine à raison de $2,4 \times 10^{-6}$ mol litre^{-1}. Les deux vaisseaux sanguins ont été décontracturés par le trimétaphan, la relaxation maximale étant obtenue à la concentration de $1,3 \times 10^{-3}$ mol litre^{-1}. Cet effet a été davantage marqué avec les bandes de veines. L'ED$_{50}$ calculé pour l'effet décontracturant du trimétaphan n'a pas été substantiellement différent dans le cas de la veine ou dans le cas de l'artère. On en a conclu que la sensibilité au trimétaphan des artères et des veines est similaire, mais que cet effet ne peut pas jouer de rôle significatif dans la production d'hypotension contrôlée.

DIREKTE WIRKUNGEN VON TRIMETAPHAN AUF DIE MESENTERIALARTERIE UND DIE VENA SAPHENA BEIM HUND

ZUSAMMENFASSUNG

Die direkten Gefässauswirkungen von Trimetaphan Camsylat auf die Mesenterialarterie und die laterale Vena saphena im Hund wurden untersucht; Gefässstreifen wurden in eine Krebs–Henseleit-Losung gehängt, und durch Phenylephrin $2,4 \times 10^{-6}$ mol litre^{-1} eine Kontraktion bewirkt. Beide Gefasse wurden durch Trimetaphan entspannt—maximal bei einer Konzentration von $1,3 \times 10^{-3}$ mol litre^{-1}; diese Wirkung war in den venösen Streifen stärker ausgeprägt. Das errechnete ED$_{50}$ für die Entspannungswirkung von Trimetaphan zeigte keinen wesentlichen Unterschied zwischen Arterie und Vene. Darus wird geschlossen, dass die Empfindlichkeit von Venen und Arterien auf Trimetaphan ähnlich ist, dass aber dieser Effekt keine wesentliche Rolle in der Hervorrufung kontrollierter Hypotension spielen kann.

EFECTO DIRECTO DEL TRIMETAFAN EN LA ARTERIA MESENTERICA Y EN LA VENA SAFENA DEL PERRO

SUMARIO

Se estudiaron los efectos vasculares directos del trimetafan camsilate en la arteria mesentérica y en la vena safena lateral del perro; se suspendieron tiras vasculares en una solución de Krebs–Henseleit y se produjeron contracciones mediante fenilefrina, $2,4 \times 10^{-6}$ mol litro^{-1}. Ambos vasos se relajaron bajo la acción del trimetafan y la máxima relajación se obtuvo a concentraciones de $1,3 \times 10^{-3}$ mol litro^{-1}; este efecto fue más marcado en las tiras de la vena. El ED$_{50}$ calculado para el efecto relajante del trimetafan no fue significativamente diferente para la arteria y la vena. La conclusión es que la sensibilidad de las arterias y de las venas al trimetafan es similar para ambas, pero que este efecto no puede jugar una función significativa en la producción de hipotensión controlada.

Br. J. Anaesth. (1980), **52**, 773

INFLUENCE OF HALOTHANE AND ENFLURANE ON RESPIRATORY AIRFLOW RESISTANCE AND SPECIFIC CONDUCTANCE IN ANAESTHETIZED MAN

J. R. LEHANE, C. JORDAN AND J. G. JONES

SUMMARY

We have developed a method for the measurement of respiratory resistance and specific airways conductance (s.G_{aw}) using the forced airflow oscillation method, and have used it to study the effects of halothane and enflurane on airway mechanics in anaesthetized patients. Resistance (R_{rs}) was determined over a range of lung volumes and s.G_{aw} was obtained by computer-aided analysis of the hyperbolic relationship between R_{rs} and lung volume. Patients received diazepam orally, followed by thiopentone and pancuronium. The trachea was intubated and the lungs ventilated with 70% nitrous oxide in oxygen. After obtaining three baseline measurements of s.G_{aw}, 1.3% halothane (10 patients) or 2.5% enflurane (10 patients) was added to the inspired gas. Halothane caused an increase in s.G_{aw} (bronchodilatation) of 47% ($P < 0.05$; paired t test) at 3 min and a non-significant increase of 72% at 15 min. Enflurane produced no significant increase in s.G_{aw} at 3 and 8 min, but a 56% increase ($P < 0.02$) at 15 min. One patient responded to halothane with an increase in bronchomotor tone, manifest by a significant reduction in s.G_{aw} ($P < 0.01$; two-sample t test). Enflurane did not cause bronchoconstriction in any patient. There was a significant reduction in resistance with halothane ($P < 0.05$; paired t test) and enflurane ($P < 0.01$). Expiratory reserve volume (ERV) was found to be small, and contributed to the high resistances observed: mean resistance 0.59 kPa litre^{-1} s, range 0.15–1.71. Small changes in ERV were also shown to produce changes in resistance independent of changes in bronchomotor tone. Neither halothane nor enflurane produced significant mean changes in ERV.

Difficulty in inflating the lungs is a well-recognized complication of general anaesthesia and is often attributed to bronchospasm (Edwards et al., 1956). The volatile anaesthetic agents are generally considered to produce bronchodilatation (Aviado, 1975) and both halothane (Colgan, 1965; Gold, 1970) and enflurane (Rodriguez and Gold, 1976) have been recommended as particularly suitable for anaesthetizing patients with obstructive lung disease. There are, however, several case reports of bronchospasm induced by enflurane (Lowry and Fielden, 1976; Schwettmann and Casterline, 1976) and one of histamine release causing severe urticaria induced by halothane (Cole, 1964).

These anaesthetic agents may affect resistance to airflow through an effect on bronchial smooth muscle or elastic recoil pressure, or both. Lung recoil pressure depends on lung volume, and the relationship between airflow resistance and lung volume is hyperbolic (Briscoe and DuBois, 1958). We have shown that changes in lung volume which occur during anaesthesia may profoundly affect resistance to airflow (Lehane, Jordan and Jones, 1979) and therefore, in any study of the effects of anaesthetics on resistance, the effect of changes in lung volume must be considered.

The effect of a change in bronchomotor tone is to modify the shape of the hyperbola that describes the resistance–volume relationship (fig. 1). At a large lung volume the large distending force exerted by lung parenchyma on the airway wall minimizes the effect of active bronchoconstriction which consequently has only a small effect on airway resistance. Conversely, at a small lung volume the small distending force on the airway wall permits active smooth muscle contraction to produce a much larger effect on airway resistance. This change in the shape of the hyperbola may be quantitated by plotting the reciprocal of resistance, conductance, against lung volume. Changes in the slope of the resulting straight line, specific airways conductance (s.G_{aw}), may be used as an index of change in bronchomotor tone (fig. 2). The advantage of this approach is that a change in functional residual capacity, for example, has no effect on the slope of the conductance–volume plot and an acute change in slope implies a change in bronchomotor activity.

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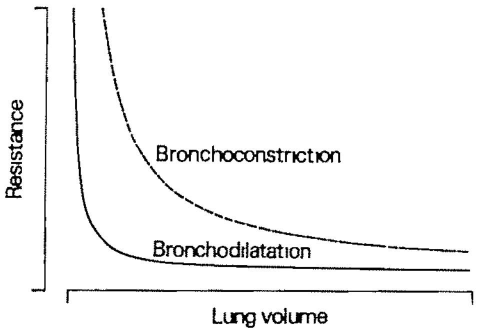

FIG. 1. Diagrammatic representation of the effect of a change in bronchomotor tone on the resistance–volume hyperbola.

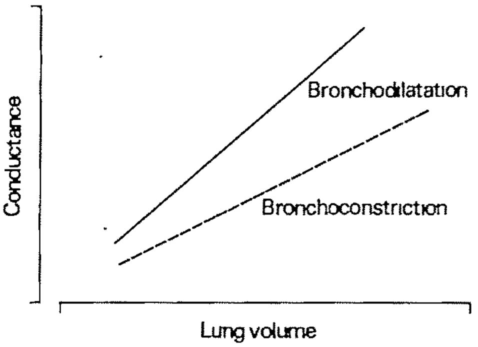

FIG. 2. Diagrammatic representation of the effect of a change in bronchomotor tone on the slope of a conductance–volume plot.

We have developed a method for measuring respiratory resistance (R_{rs}) and s.G_{aw} which is suitable for use during anaesthesia in man. This paper presents the results of a study of the effects of halothane and enflurane on R_{rs} and s.G_{aw} in anaesthetized patients.

METHODS

Patients

The study was approved by the Northwick Park Hospital Ethics Committee, and informed consent was obtained from each patient. Twenty patients aged between 18 and 60 yr were studied. They were not receiving any drugs and were non-smokers. There was no evidence of convulsive disorder, or of cardiac or respiratory disease. The patients were undergoing routine surgical procedures requiring general anaesthesia with tracheal intubation and neuromuscular blockade. They were randomly allocated to two groups of 10, one group to receive halothane, the other enflurane.

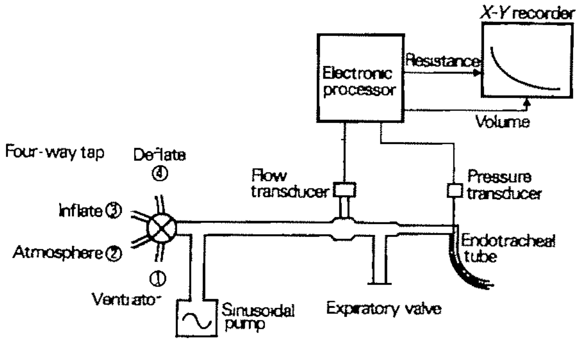

FIG. 3. General arrangement of circuit showing positions of four-way tap and location of sinusoidal pump, pneumotachograph and expiratory valve. Pressure and flow data are processed to give a resistance–volume plot.

Resistance–volume plots

Plots of total respiratory resistance (R_{rs}) against volume over part of the vital capacity range were obtained using the modified anaesthetic circuit shown in figure 3. A tap was fitted to a Manley ventilator so that mechanical ventilation could be interrupted and replaced by a slow inflation or deflation of 3 litre min^{-1}. The forced airflow oscillation method (Goldman et al., 1970; Hyatt et al., 1970) was used to measure R_{rs} during the deflation manoeuvre. The oscillating airflow was produced by a purpose-built, sinusoidal pump (developed by Division of Bioengineering, CRC, Harrow) delivering a stroke volume of 58 ml at a frequency of 3 Hz. Airway pressure was sensed with a pressure transducer (Pye Ether UP2) via a catheter the tip of which was at the distal end of the tracheal tube. A flow signal was obtained using a heated Fleisch No. 2 pneumotachograph and differential pressure transducer (Validyne MP 45-1). The pressure and flow signals were analysed electronically and R_{rs} and the change in lung volume were derived. R_{rs} was plotted as a function of lung volume on an X–Y recorder (Bryans 26000). The volume range studied was from 1 litre greater than FRC to near residual volume.

Specific airways conductance

Plots of conductance against volume may be obtained from the corresponding resistance–volume plots. However, the conductance–volume plot will be linear only if resistance tends to zero at large lung volume. It was necessary, therefore, to subtract the contributions to R_{rs} which do not tend to zero at large lung volumes. This residual resistance may include the resistances of upper airway, lung tissue and chest wall. We were able to exclude upper airway resistance by measuring airway pressure at the tip of the tracheal tube, but as it was not practical to measure alveolar pressure it was not possible to exclude lung tissue resistance. A computer-aided curve-fitting routine was therefore used to fit a hyperbola to the resistance–volume data in order to determine the residual or asymptotic resistance and to enable the derivation of specific airways conductance.

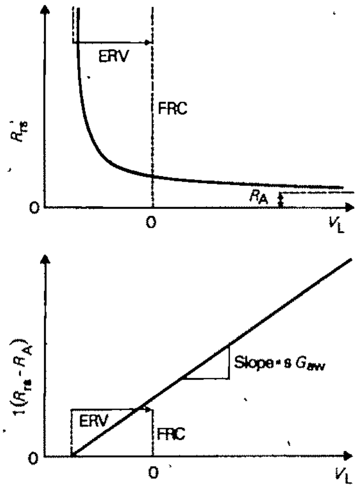

FIG. 4. Diagram of the resistance and conductance curves to show R_A, ERV and s.G_{aw} (see text).

Computer analysis

The resistance–volume curves were sampled at 0.02-litre increments using a D–MAC digitizing table and stored on paper tape. The data were analysed by computer to derive the parameters of the hyperbola fitted to each plot. The three parameters derived (fig. 4) were asymptotic resistance (R_A), asymptotic volume (ERV, see below) and specific conductance (s.G_{aw}) where:

$$1/(R_{rs}-R_A) = \text{s.}G_{aw} \times (V_L + \text{ERV}) \quad (1)$$

and:

$V_L = 0$ at FRC where V_L is lung volume

R_A represents the component of R_{rs} which does not vary with lung volume (*viz.* resistance of lung tissue and chest wall). $(R_{rs}-R_A)$ is the resistance of the distensible intrathoracic airways, and $1/(R_{rs}-R_A)$ is the conductance of these distensible airways. s.G_{aw} is the slope of the plot of the conductance of these airways against V_L over the range of V_L. In this method s.G_{aw} is derived directly from the analysis of the hyperbolic plot of R_{rs} and V_L.

The mean respiratory resistance over a tidal volume of 0.7 litre (R_{V_T}) was calculated from the area under the fitted hyperbolic curve between the end-expiratory volume point and 0.7 litre above this point:

$$R_{V_T} = \int_0^{0.7} R_{rs}\, dV_L/0.7 \quad (2)$$

Expiratory reserve volume (ERV) is conventionally measured as the volume expired by a maximal expiratory effort from FRC. In this study ERV was defined as the volume asymptote of the R_{rs}–V_L plots, which is the volume at which resistance could be infinite. This represents the maximum volume that could be expelled from the lung following the application of a large subatmospheric pressure to the airway of a paralysed patient and is likely to be larger than the ERV determined by spirometry.

Full details of the method, including the computer analysis, will be presented elsewhere (Jordan et al., in preparation).

Procedure

Premedication was with diazepam 0.2 mg kg^{-1} orally. Anaesthesia was induced with thiopentone 3.5–4 mg kg^{-1} i.v. and maintained with 70% nitrous oxide in oxygen. Pancuronium 0.12 mg kg^{-1} provided neuromuscular blockade. After tracheal intubation, ventilation was adjusted to maintain end-tidal $P\text{CO}_2$ at 5 kPa (measured with a Godart infra-red analyser corrected for the effects of nitrous oxide).

At least three baseline resistance–volume plots were obtained during the following 15 min. Ten patients subsequently received 1.3% halothane and 10 received 2.5% enflurane. Inspired and end-tidal concentrations of the volatile agents were measured using a mass spectrometer (BOC Medishield). At least three further resistance–volume plots were obtained during the following 15 min.

All the measurements were completed before the commencement of surgery.

Statistical analysis

Following the introduction of both volatile agents, the degree of change in both resistance and specific conductance was found to be dependent on the initial values. After logarithmic transformation, the differences in these variables were found to be normally distributed and independent of the initial values. Statistical analyses of changes in R_{V_T} and s.G_{aw} were therefore performed on the logarithmic data and Student's *t* tests were applied.

RESULTS

Patients in the two groups were well matched for age, weight and height (table I). There were no significant differences in end-tidal concentration of the volatile anaesthetics when expressed as a fraction of minimal alveolar concentration (MAC assumed to be 0.8% halothane and 1.68% enflurane) during the period of measurement (fig. 5).

TABLE I. *Anthropometric data* (SD); *two groups of* 10 *patients*

	Halothane	Enflurane
Females	6	8
Mean age (yr)	42.6 (11.5)	42.9 (9.8)
Mean weight (kg)	72.1 (11.6)	67.5 (12.6)
Mean height (cm)	168 (11)	167 (10)
Per cent of average weight for height and age	107 (17)	101 (14)

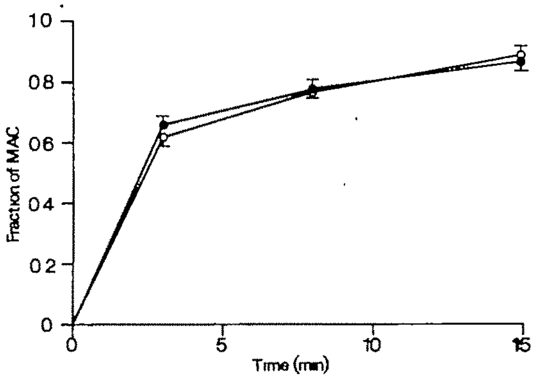

FIG. 5. Mean end-tidal concentration (± SEM), expressed as a fraction of 1 MAC for halothane (○) and enflurane (●).

Resistance–volume plots

Typical plots are shown for two patients in figure 6A and B. These illustrate the hyperbolic relationship between resistance and volume and also show the effects of halothane administration. In both cases there was a reduction in resistance over the tidal volume range (R_{V_T}) following halothane administration. In figure 6A, there was only a small increase in ERV (20 ml) and the reduction in R_{V_T} from 0.68 to 0.22 kPa litre^{-1} s resulted mainly from a change in the shape of the curve. This shape change was a result of a change in bronchomotor tone, with s.G_{aw} increasing from 4.56 to 28.8 kPa^{-1} s^{-1}. In figure 6B, R_{V_T} changed from 0.73 to 0.27 kPa litre^{-1} s and there was displacement in the curve to the left which resulted in ERV increasing by 0.2 litre. This volume change accounted for most of the reduction in R_{V_T}, but there was also a decrease in bronchomotor tone with s.G_{aw} increasing from 6.21 to 19.9 kPa^{-1} s^{-1}.

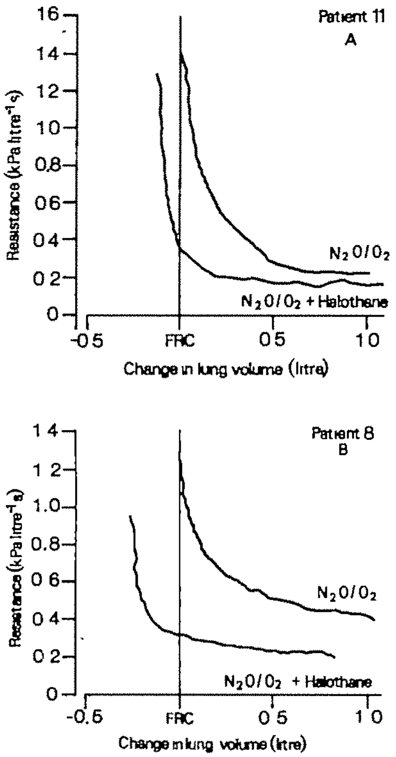

FIG. 6. A: The effect of halothane in one patient to show a small change in ERV and a large change in respiratory resistance. The decrease in resistance over the tidal range (R_{V_T}) is almost entirely a result of reduction in bronchomotor tone. B: A different patient illustrates another mechanism for a decrease in respiratory resistance following addition of halothane. The decrease in resistance is accounted for largely by an increase in ERV, together with an independent reduction in bronchomotor tone.

Specific conductance

Figure 7 shows mean changes in $\log_e$ s.G_{aw} from the baseline derived from mean values obtained during nitrous oxide anaesthesia. Administration of both halothane and enflurane was accompanied by an increase in s.G_{aw} indicating bronchodilatation, which was significant for halothane at 3 min ($P < 0.05$) and for enflurane at 15 min ($P < 0.02$, paired t test).

The responses of the individual patients to halothane and enflurane are shown in figure 8A, B. There was considerable variability in response to both agents at 3 min and this variability subsequently increased with halothane, and reduced with enflurane.

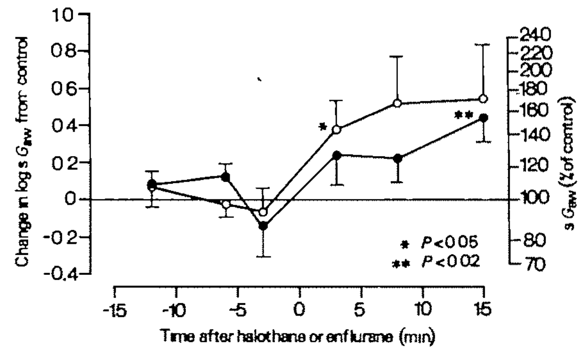

FIG. 7. Mean changes in s.G_{aw} from baseline values during nitrous oxide anaesthesia. The left y-axis indicates difference in $\log_e$ s.G_{aw}, and the right y-axis, the antilog of the left y-axis, indicates percentage change in s.G_{aw} (halothane (○) and enflurane (●), ± SEM).

The two-sample t test, applied to the data from each patient individually, showed significant increases in s.G_{aw} in six of 10 patients given halothane and three of 10 given enflurane. In one patient given halothane there was a significant decrease in s.G_{aw} ($P<0.01$), but in no patient given enflurane was there a significant decrease in s.G_{aw}.

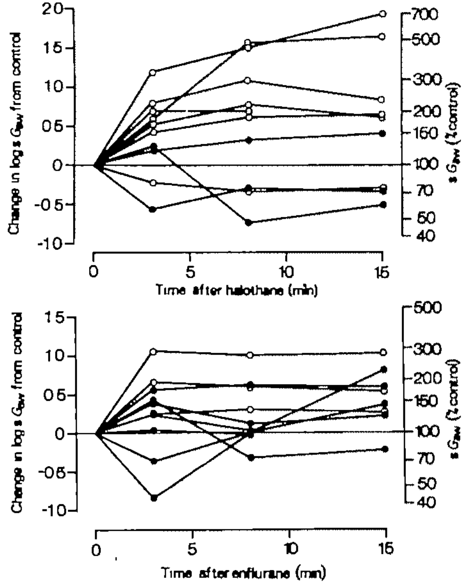

FIG. 8. A: Changes in s.G_{aw} in each patient with halothane. (○ = significant change, $P<0.05$); B: Changes in s.G_{aw} in each patient with enflurane. (○ = significant change, $P<0.05$.)

Mean resistance over the tidal volume range ($\bar{R}_{V_T}$)

Figure 9 shows mean respiratory resistance over the tidal volume range (R_{V_T}) before and during the administration of halothane and enflurane for individual patients. Halothane produced a significant mean decrease of 30% (change in $\log_e$ R_{V_T} from control = 0.36, SEM 0.15, $P<0.05$, paired t test) and enflurane produced a mean decrease of 20% (change in $\log_e$ R_{V_T} = 0.22, SEM 0.06, $P<0.01$).

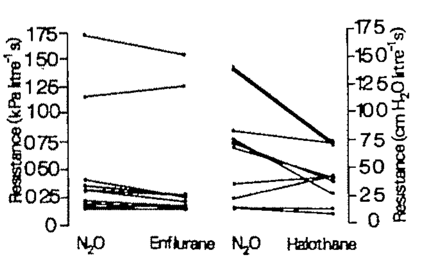

FIG. 9. Respiratory resistance (R_{V_T}) before and during administration of halothane and enflurane in individual patients.

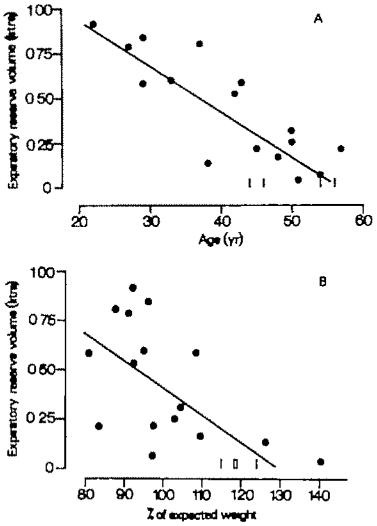

FIG. 10. A: Correlation between ERV during anaesthesia and age of patient. (I = ERV < 0.05 litre.) B: Correlation between ERV and % of normal expected weight. (I = ERV < 0.05 litre.)

Expiratory reserve volume (ERV)

There were no significant mean group changes in ERV following the introduction of either volatile agent. Halothane was associated with an increase in ERV in three patients (+0.055, +0.075 and +0.350 litre), and a decrease in four (−0.035, −0.040, −0.045 and −0.109 litre). Enflurane was associated with an increase in four patients (+0.030, +0.040, +0.060 and +0.100 litre), and a decrease in two

(−0.080 and −0.095 litre). During nitrous oxide in oxygen anaesthesia ERV was less than 0.25 litre in 10 of the 20 patients. There was a significant negative correlation with age ($P < 0.01$) (fig. 10A) and with weight ($P < 0.05$) (fig. 10B) when the latter was expressed as a percentage of average weight for age and height.

DISCUSSION

This is the first study of airflow resistance in anaesthetized patients to distinguish between the effects of changes in bronchomotor tone and changes in lung volume. The resistance–volume plots obtained in this study confirm, in anaesthetized patients, the hyperbolic relationship previously described for conscious man (Briscoe and DuBois, 1958). This hyperbolic relationship has a number of important implications. First, it is clear that changes in lung volume such as are known to occur during anaesthesia may produce very large changes in respiratory resistance without the need to invoke changes in bronchomotor tone. Second, the magnitude of the effect of any given change in lung volume on resistance is dependent on the initial lung volume so that, at small lung volumes, small changes in volume will have a much greater effect on resistance than the same change at a larger lung volume. Third, the magnitude of the effect of a change in bronchomotor tone is also dependent on lung volume so that, at large lung volumes, even large changes in s.G_{aw} produce only small changes in resistance, whereas, at small lung volumes, small changes in s.G_{aw} may produce large changes in resistance. This is illustrated in figure 11 which shows the effect of three levels of bronchomotor tone at large and small ERV. It will be seen that, at any given s.G_{aw}, resistance is greater at the smaller ERV and that the difference in resistance produced by a change in s.G_{aw} is greater at small lung volume. Therefore it is essential to take account of the effect of lung volume whenever lung volumes are small and to note that when bronchospasm complicates general anaesthesia a small lung volume is likely to make an important contribution to airflow resistance.

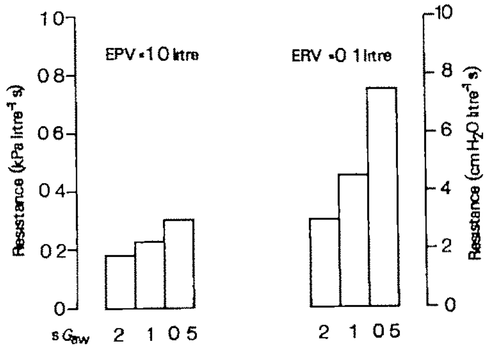

FIG. 11. The effect of large and small ERV on resistance as bronchomotor tone increases (s.G_{aw} decreasing from 2 to 0.5).

The expiratory reserve volumes observed in this study were very small. Whilst it is known that a change in posture from erect to supine produces a reduction in ERV (Blair and Hickham, 1955), it is not known whether the small ERV measured in our anaesthetized patients resulted from the supine posture, the state of anaesthesia or both these factors. It is established that anaesthesia usually causes a decrease in functional residual capacity (Hewlett et al., 1974a, b) which must also further reduce ERV if residual volume remains constant. The possibility that ERV is reduced during anaesthesia remains unconfirmed in individual patients in this study because measurements of ERV were not made in the conscious supine state. Obesity and advancing age are both known to be associated with reduction in ERV (Cotes, 1979) and in our study during anaesthesia the ERV in patients more than 50 yr, or more than 110% of average weight, was less than 0.25 litre. The addition of halothane or enflurane produced no significant mean changes in ERV in the grouped data, but the small changes which occurred in individual patients were sufficient to produce important changes in airflow resistance because of the small initial ERV. This effect of anaesthesia on ERV in some subjects, while of considerable interest in terms of its effects on lung mechanics and gas exchange, is not easily explained. A possibility is that changes in central blood volume may cause a change in thoracic gas volume (Jones et al., 1979). It is clearly important to make measurements of ERV and FRC with and without volatile agents to attempt to elucidate this mechanism.

There can be no doubt that, in most patients, bronchomotor tone was substantially reduced by the administration of halothane and enflurane, although one patient given halothane showed a significant decrease in s.G_{aw} indicating bronchoconstriction. The effect of enflurane was smaller but more consistent than that of halothane. Although the average response was a reduction in bronchomotor tone, the decrease in resistance which occurred was not completely accounted for by these changes in tone. Paradoxically, in some patients, there was an increase in bronchomotor tone which was not accompanied by an increase in resistance. This paradox is fully explained by the increase in ERV which occurred in these patients and which was sufficient to increase airway calibre and offset the effect of bronchomotor tone. In one patient given halothane, the opposite effect was noted in that an increase in s.G_{aw} failed to reduce resistance because there was a concomitant reduction in ERV. These results emphasize the importance of determining the effects of changes in lung volume if changes in airway resistance are to be interpreted.

The observation that halothane reduces airways resistance in man is broadly in agreement with the findings of Rügheimer, Himmler and Greiner (1974), Rolly and Thomas (1975) and Morr-Strathmann, Welter and Lawin (1977), but conflicts with the findings of Patterson and others (1968) and Brakensiek and Bergman (1970). Our finding that enflurane also reduces resistance is in agreement with those of Rolly and Thomas (1975) and Morr-Strathmann, Welter and Lawin (1977), but is in conflict with the finding of Rügheimer, Himmler and Greiner (1974). The differences in the results are most likely to be a result of methodological differences in resistance measurement, and the failure of other workers to take into account the effects of changes in lung volume.

Attempts to elucidate the mechanism of action of halothane on bronchomotor tone in animals and man have also yielded conflicting results. It has been suggested that halothane causes bronchodilatation. Klide and Aviado (1967) found evidence in intact dogs that this was mediated by beta-adrenergic stimulation, whereas Fletcher, Flacke and Alper (1968), using isolated guineapig trachea, and Hickey and others (1969), using intact dogs, concluded that it was a result of a non-specific direct effect on the smooth muscle cell. Fletcher, Flacke and Alper (1968) found that the relaxation in isolated guineapig tracheal muscle was not blocked by beta-adrenergic blockade, whereas Boissier and others (1968) found that, in guineapig lung *in situ*, beta blockade gave a bronchoconstrictor effect with halothane. Brakensiek and Bergman (1970) and Patterson and others (1968) found that halothane produced little effect on bronchial smooth muscle activity in anaesthetized patients although Meloche and others (1969), in a study similar to that of Patterson and his co-workers, found that halothane caused bronchodilatation. Even if there were no species differences it would not be possible to produce from these results a unified hypothesis from which changes in R_{rs} could be predicted. In the studies which used intact lungs it was assumed that the effects of recoil pressure would not affect comparisons of airway resistance or calibre. Indeed, it has been suggested recently that recoil pressure is not normally amenable to change with drugs and that, therefore, drug-induced changes in bronchial calibre can be attributed to effects on bronchial smooth muscle alone (Tattersfield, 1979). Our results show that, during anaesthesia in man, such an assumption is unwarranted.

In conclusion, we have developed a method for the measurement of changes in bronchomotor tone which allows for the effect of lung recoil pressure. We have used the method to study the effects of halothane and enflurane on the airways of anaesthetized patients. Both agents produced significant bronchodilatation, although the effect of halothane was more marked than that of enflurane. Changes in lung volume sometimes reversed the effects of changes in bronchomotor tone. There was much greater variability in response to halothane and one patient showed significant bronchoconstriction with this agent.

ACKNOWLEDGEMENTS

We would like to thank Anne Rhodes for digitizing the data, the C.R.C. Division of Computing and Statistics for help in data analysis, Abbott Laboratories for supplies of enflurane and Brenda Dobson and Norma Saunders for secretarial help.

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INFLUENCE DE L'HALOTHANE ET DE L'ENFLURANE SUR LA RESISTANCE DU DEBIT D'AIR RESPIRATOIRE ET SUR LA CONDUCTIVITE SPECIFIQUE CHEZ L'HOMME ANESTHESIE

RESUME

Nous avons mis au point une méthode permettant de mesurer la résistance respiratoire et la conductivité spécifique des voies respiratoires (s.G_{aw}) grace à la méthode d'oscillation du débit d'air forcé et nous nous en sommes servis pour étudier les effets de l'halothane et de l'enflurane sur la mécanique des voies respiratoires de malades anesthésiés. La résistance (R_{rs}) a été déterminée sur une plage de volumes de poumons et on a obtenu s.G_{aw} par une analyse de la relation hyperbolique qui existe entre R_{rs} et le volume des poumons, effectuée à l'aide d'un ordinateur. On a administré de diazépam aux malades par voie buccale; ceci a été suivi de thiopentone et de pancuronium, puis on a intubé la trachée et ventilé les poumons à l'aide de 70% de protoxyde d'azote dans de l'oxygène. Après avoir obtenu trois mesures de la ligne zéro de s.G_{aw}, on a ajouté au gaz inspiré 1,3% d'halothane (sur 10 malades) ou 2,5% d'enflurane (sur 10 malades). L'halothane a entraîné une augmentation de 47% de s.G_{aw} (bronchodilatation) ($P < 0,05$; couplé avec le test t) à 3 min, ainsi qu'une augmentation sans signification de 72% à 15 min. L' enflurane n'a produit aucune augmentation d'importance dans la s.G_{aw} à 3 et à 8 min, mais une augmentation de 56% à 15 min ($P < 0,02$). Un malade a réagi à l'halothane par une augmentation de la tonicité bronchomotrice, qui s'est manifestée par une réduction significative de s.G_{aw} ($P < 0,01$; avec test t sur deux échantillons). L'enflurane n'a causé de constriction des bronches sur aucun malade. Il y a eu une réduction significative de la résistance avec l'halothane ($P < 0,05$; couplé avec le test t) et l'enflurane ($P < 0,01$). Le volume expiratoire de réserve (ERV) a été trouvé petit, et a contribué aux hautes résistances que l'on a observées: résistance moyenne 0,59 kPa litre^{-1} s, plage de 0,15–1,17. De petites variations dans l'ERV ont aussi produit des variations dans la résistance, indépendantes des variations dans la tonicité bronchomotrice. Ni l'halothane, ni l'enflurane n'ont produit de variations moyennes significatives dans l'ERV.

DER EINFLUSS VON HALOTHAN UND ENFLURAN AUF DEN ATEMSTROMWIDERSTAND UND SPEZIFISCHE LEITFÄHIGKEIT BEI NARKOTISIERTEN PATIENTEN

ZUSAMMENFASSUNG

Wir entwickelten eine Methode zur Messung des Atemwiderstandes und der spezifischen Leitfahigkeit der Luftwege (s.G_{aw}) unter Verwendung der forcierten Luftstrom-Oszillationsmethode; damit haben wir die Auswirkungen von Halothan und Enfluran auf auf die Mechanik der Luftwege bei narkotisierten Patienten studiert. Der Widerstand (R_{rs}) wurde uber einen Bereich von Lungenvolumen bestimmt, und s.G_{aw} wurde durch eine Analyse mit Komputerhilfe der hyperbolischen Beziehung zwischen R_{rs} und Lungenvolumen erzielt. Die Patienten erhielten oral Diazepam, gefolgt von Thiopenton und Pancuronium. Dir Trachea wurde intubiert, und die Lungen wurden mit 70% Stickoxyd in Sauerstoff beluftet. Nach Feststellung der drei Grundmessungen von s.G_{aw} wurden dem eingeatmeten Gas 1,3% Halothan (10 Patienten) oder 2,5% Enfluran (10 Patienten) hinzugefugt. Halothan bewirkte einen Anstieg von s.G_{aw} (Bronchialerweiterung) von 47% ($P<0,05$; paariger *t*-Test) nach 3 min, und einen nicht wesentlichen Anstieg von 72% nach 15 min. Enfluran bewirkte nach 3 und 8 min keinen Anstieg, aber einen Anstieg von 56% ($P<0,02$) nach 15 min. Ein Patient reagierte auf Halothan mit einem Anstieg des bronchomotorischen Tons, manifestiert durch eine wesentliche Reduktion von s.G_{aw} ($P<0,01$; *t*-Test mit zwei Proben). Enfluran bewirkte bei keinem Patienten Bronchialverengung. Es kam zu einer wesentlichen Widerstandsverringerung bei Halothan ($P<0,05$; paariger *t*-Test) und Enfluran ($P<0,01$). Ausatmungsreservevolumen (ERV) war klein, und trug zu dem hohen beobachteten Widerstand bei: mittlerer Widerstand 0,59 kPa Liter^{-1} s, Bereich 0,15–1,71. Leine Veranderungen in ERV riefen Widerstandsveranderungen unabhängig von den Veränderungen des bronchomotorischen Tons hervor. Weder Halothan noch Enfluran bewirkte signifikante Veränderungen in ERV.

INFLUENCIA DEL HALOTANO Y ENFLURANO EN LA RESISTENCIA DEL FLUJO DE AIRE RESPIRATORIO Y LA CONDUCTABILIDAD ESPECIFICA EN EL SER HUMANO ANESTESIADO

SUMARIO

Hemos elaborado un método de medición de la resistencia respiratoria y de la conductabilidad específica de las vías respiratorias (s.G_{aw}) al usar el método de oscilación del flujo de aire forzado, el cual hemos empleado para estudiar los efectos del halotano y enflurano sobre la mecánica de las vías respiratorias en pacientes anestesiados. Se determinó la resistencia respecto de una serie de volúmenes pulmonares y se obtuvo s.G_{aw} mediante un análisis por computadora de la relación hiperbólica entre R_{rs} y el volumen del pulmón. Se administró diazepam oralmente a los pacientes, seguido por tiopentona y pancuronio. Se les intubó la tráquea y se les ventiló los pulmones mediante oxído nitroso al 70% en oxígeno. Después de obtener tres mediciones básicas del s.G_{aw}, se añadió al gas inspirado halotano al 1,3% (10 pacientes) o enflurano al 2,5% (10 pacientes). El halotano causó un aumento del s.G_{aw} (broncodilatación) de un 47% ($P<0,05$; ensayo *t* emparejado) a los 3 min y un incremento insignificante del 72% a los 15 min. El enflurano no produjo aumento significativo del s.G_{aw} a los 3 y 8 min, pero sí un incremento del 56% ($P<0,02$) a los 15 min. Un paciente tuvo una respuesta al halotano que resultó en un aumento del tono broncomotor que se manifestó por una disminución significante del s.G_{aw} ($P<0,01$; ensayo *t* sobre dos muestras). El enflurano no provocó ninguna bronco-constricción en ninguno de los pacientes. Hubo una reducción significativa de la resistencia con el halotano ($P<0,05$; ensayo *t* emparejado) y con el enflurano ($P<0,01$). El volumen del aire de reserva (VAR) comprobó ser bajo y contribuyó a las altas resistencias observadas: la resistencia media era de 0,59 kPa litro^{-1} s, extensión de 0,15–1,71. Pequeñas alteraciones del VAR también produjeron cambios en la resistencia, independientes de las variaciones del tono broncomotor. Ni el halotano ni el enflurano produjeron cambios medios significativos en el VAR.

Br. J. Anaesth. (1980), **52**, 783

RELATIVE POTENCY OF ORG NC 45, PANCURONIUM, ALCURONIUM AND TUBOCURARINE IN ANAESTHETIZED MAN

N. KRIEG, J. F. CRUL AND L. H. D. J. BOOIJ

SUMMARY

The relative potency, time-course of action and cardiovascular effects of Org NC 45, a new non-depolarizing neuromuscular blocking agent, have been compared with those of pancuronium, alcuronium and tubocurarine in 64 anaesthetized patients. The relative potency (ED_{50}) to Org NC 45 was 1.74, 3.69 and 8.57 respectively. In doses which caused useful surgical relaxation, duration of action of Org NC 45 was 34%, 39% and 26% that of pancuronium, alcuronium and tubocurarine. After administration of repeated doses no cumulation was seen for Org NC 45. The new drug was free from any effect on arterial pressure and heart rate.

Org NC 45, the monoquaternary homologue of pancuronium, is a non-depolarizing neuromuscular blocking agent. It was shown to be a short-acting drug with fast onset of action. The absence of the acetylcholine-like fragment in the A-ring of the molecule made it devoid of vagolytic action while the preservation of the D-ring configuration contributed to the maintenance of strong curariform potency (Buckett, Hewett and Savage, 1973; Savage, Sleight and Carlyle, 1980). In animal experiments its neuromuscular blocking properties have been characterized by a short time to peak effect, a short duration of action and a fast recovery of the neuromuscular block (Durant et al., 1979). A comparative study with other non-depolarizing agents in dogs (Booij et al., 1980) indicated that Org NC 45 was almost free from cardiovascular side-effects. First clinical trials (Crul and Booij, 1980) were very promising and confirmed the impression that most of the properties of Org NC 45 found in animals were valid in man. We have compared neuromuscular blocking and cardiovascular effects of Org NC 45 with those of pancuronium, alcuronium and tubocurarine, the most commonly used relaxants. We investigated relative potency by means of cumulative dose-response curves and by titrated 95% neuromuscular blocking doses. In the second part of the study effects and side-effects of equipotent bolus injections of the four drugs were studied.

METHODS

Healthy patients undergoing elective lower limb or abdominal surgery, and who had given consent to the study, were premedicated with atropine 0.25 mg, droperidol 5 mg and piritramide 0.15 mg kg^{-1} i.m., 45 min before anaesthesia. Induction was with thiopentone 5 mg kg^{-1} i.v. and anaesthesia was maintained with 67% nitrous oxide in oxygen and incremental doses of fentanyl as needed. A Grass S 88 nerve stimulator delivered supramaximal stimuli at a rate of 0.1 Hz and of 0.2 ms duration, via thin-wall needle electrodes placed subcutaneously over the ulnar nerve near the wrist. Adduction force of the thumb was quantified with a Statham UC 3 force displacement transducer and recorded on a polygraph together with heart rate taken from e.c.g.

Part A

Twenty patients (mean age 46 ± 3 yr; body weight 66 ± 2 kg) were randomly allocated to four groups. After induction of anaesthesia and the injection of suxamethonium 1 mg kg^{-1} i.v., the trachea was intubated. When the depression of twitch tension had recovered completely for at least 5 min, cumulative doses of constant amounts of Org NC 45, pancuronium, alcuronium or tubocurarine i.v. were given till nearly 95% depression of twitch tension was obtained. Incremental doses were administered when the twitch height remained constant for three consecutive twitches. When about 95% depression was reached the neuromuscular blockade

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0007-0912/80/080783-06 $01.00

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was allowed to recover spontaneously. At 25% of control twitch tension one-quarter of the total cumulative dose was administered i.v. as a maintenance dose (individual maintenance dose). The maintenance dose was repeated, whenever 25% of control twitch height returned, until the end of the surgical procedure. The mean of total cumulative doses of each relaxant tested was calculated as the mean dose resulting in a 95% depression (titrated ED_{95}).

Part B

Forty-four patients (mean age 37 ± 2 yr; body weight 66 ± 1 kg) were randomly divided into four groups. In half the number in each group the trachea was intubated as described in part A. After recovery from suxamethonium, which took between 9 and 14 min, and stable twitch response over 5 min, the tritrated ED_{95} dose (part A) of Org NC 45, pancuronium, alcuronium or tubocurarine was administered i.v. as a bolus. In the remaining patients of each group the trachea was intubated after administration of the "titrated ED_{95}" doses, without prior suxamethonium administration, when thumb twitch depression had reached its maximum—between 4 and 12 min.

Arterial pressure was monitored carefully immediately before and 2, 5, 15 and 30 min after the bolus injection of neuromuscular blockers. Patients in this group showing large changes in arterial pressure or heart rate (being obviously a result of intubation) were excluded from the study.

Cumulative dose–response curves were constructed by means of linear regression analysis and compared statistically by an analysis of covariance (Neter and Wasserman, 1974). Student's *t* test was applied to compare time from the end of the injection of the neuromuscular blocker to maximal effect (onset), time from end of injection until recovery of the twitch height to 25% and 90% of control (duration 25, duration 90), time elapsed from 25% to 75% twitch response (recovery index) and changes in heart rate and arterial pressure. Statistically significant differences were assumed at $P < 0.05$.

RESULTS

Part A

The cumulative dose–response curves of the four relaxants differed from each other, but were parallel (fig. 1). Taken from ED_{50}, calculated by linear regression, the ratio of potency Org NC 45 : pancuronium : alcuronium : tubocurarine was 1 : 1.74 : 3.69 : 8.57. Mean titrated ED_{95} of the four drugs are given in table I. The potency ratio of these 95% blocking doses was 1 : 1.72 : 3.9 : 9.43. The individual

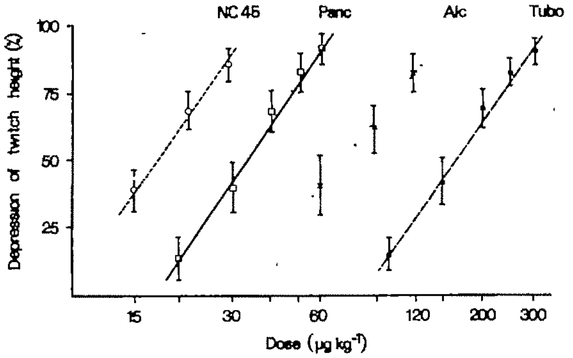

FIG. 1. Cumulative dose–response curves of Org NC 45, pancuronium, alcuronium and tubocurarine (five patients in each group).

TABLE I. *Mean cumulative doses of relaxants to produce a 90–95% depression of twitch height (mean ± SEM)*

Drug	Dose (μg kg⁻¹)	% Block	*n*
Pancuronium	62.2 ± 4.9	95.1 ± 0.8	5
Alcuronium	140.8 ± 12.4	93.4 ± 2.0	5
Tubocurarine	340.6 ± 36.9	95.3 ± 0.6	5
Org NC 45	36.1 ± 5.7	92.4 ± 0.9	5

TABLE II. *Time-course of maintenance of neuromuscular blockade. Doses amounted to one-quarter of individual 95% blocking dose. Duration 25 was significantly prolonged after the third injection of pancuronium, alcuronium and tubocurarine. It remained constant for Org* NC 45 (P < 0.05; *mean ± SEM*).

		First repeat		Second repeat		
Drug	Dose (μg kg⁻¹)	% Block	Duration 25 (min)	% Block	Duration 25 (min)	*n*
Pancuronium	15.6 ± 1.2	89.7 ± 2.0	25.9 ± 6.8	94.4 ± 0.6	34.4 ± 6.7	5
Alcuronium	35.2 ± 3.1	94.6 ± 1.5	27.5 ± 2.8	94.1 ± 2.5	33.2 ± 4.5	5
Tubocurarine	85.2 ± 9.2	92.1 ± 0.9	38.3 ± 7.5	91.6 ± 2.3	42.3 ± 8.6	5
Org NC 45	9.0 ± 1.4	87.9 ± 2.0	8.0 ± 0.7	87.1 ± 1.2	8.5 ± 0.8	5

maintainance dose caused statistically identical reductions of thumb twitch response in all groups (table II). The recovery time to 25% of control twitch tension (duration 25) was significantly longer after the second maintenance dose of pancuronium, alcuronium and tubocurarine compared with the first dose (table II). For Org NC 45 duration 25 did not change significantly over a series of four injections: 8.1 ± 1.0 and 9.0 ± 0.8 after the third and fourth repeat dose respectively.

Part B

Mean neuromuscular blockade achieved by bolus injection of the titrated ED$_{95}$ was smaller than that of the cumulative administration. The difference was not statistically significant. The blocking effect of the bolus injections was identical comparing the patients within groups (with and without prior suxamethonium) and between groups (table III). Onset, duration and recovery index of neuromuscular blockade are shown in table IV. Onset was equal in the Org NC 45 and pancuronium groups. All other time-courses of action were significantly shorter for Org NC 45.

Pancuronium, alcuronium and tubocurarine increased heart rate significantly in the first 5 min after administration, whereas heart rate in the Org NC 45 group remained unchanged. Arterial pressure decreased significantly after alcuronium and tubocurarine and increased after pancuronium; however, the last effect was not statistically significant. Patients who received Org NC 45 showed no significant change in arterial pressure (fig. 2).

DISCUSSION

The relative potency of pancuronium, alcuronium and tubocurarine found in this study is in accord with previous animal studies (Cass et al., 1976; Booij et al., 1980) and human studies (Lund and Stovner, 1970; Donlon, Ali and Savarese, 1974) and with clinical experience (Baird and Reid, 1967; Baird, 1968; Crul, 1970; Levin and Dillon, 1971). Somogyi, Shanks and Triggs (1978) calculated the amount of a bolus injection of pancuronium producing an almost complete block to be 62.5 μg kg^{-1} body weight. This is almost identical with our finding (62.2 ± 4.9 μg kg^{-1}).

The relative potency of Org NC 45 to pancuronium (1.7) in this study differs from that reported by Agoston and others (1980), who found the drugs to be equipotent. The difference may be explained by differences in method. We facilitated intubation of the trachea with suxamethonium 1.0 mg kg^{-1} before titration of the 95% blocking dose by steps, whereas Agoston's group administered bolus injections of Org NC 45 without prior suxamethonium. The influence of suxamethonium on the potency of subsequently given non-depolarizing neuromuscular blocking agents is contested (Walts and Dillon, 1969; Katz, 1971; Walts and Rustin, 1977). We did not observe a significant influence on pancuronium, alcuronium and tubocurarine (Walts and Rustin, 1977), but prior administration of suxamethonium seems to enhance the neuromuscular blocking effect of Org NC 45 (table III).

TABLE III. *Percent neuromuscular blockade after bolus injection of non-depolarizing relaxant, with and without previous suxamethonium 1 mg kg^{-1} and both groups combined (mean ± SEM)*

Drug	Dose (μg kg^{-1})	% Block Without	 With sux.	 All	n
Pancuronium	62	92.9 ± 3.5	84.6 ± 6.9	88.7 ± 3.9	12
Alcuronium	141	84.4 ± 4.9	79.9 ± 11.9	82.1 ± 6.1	10
Tubocurarine	341	84.4 ± 3.8	83.2 ± 5.1	83.8 ± 3.0	10
Org NC 45	36	78.8 ± 6.5	90.7 ± 4.1	83.8 ± 4.1	12

TABLE IV. *Time-course of neuromuscular blockade in patients after a bolus injection of relaxant (mean ± SEM)*

Drug	Dose (μg kg^{-1})	Onset (min)	Duration 25 (min)	Duration 90 (min)	Recovery index (min)	n
Pancuronium	62	4.9 ± 0.7	34.4 ± 5.8	73.2 ± 11.4	31.9 ± 4.5	12
Alcuronium	141	5.9 ± 0.4	29.3 ± 1.6	62.6 ± 7.5	29.0 ± 2.3	10
Tubocurarine	341	9.9 ± 1.1	33.8 ± 4.3	96.4 ± 16.1	59.3 ± 8.1	10
Org NC 45	36	4.5 ± 0.2	11.6 ± 1.2	24.9 ± 2.4	9.7 ± 0.8	12

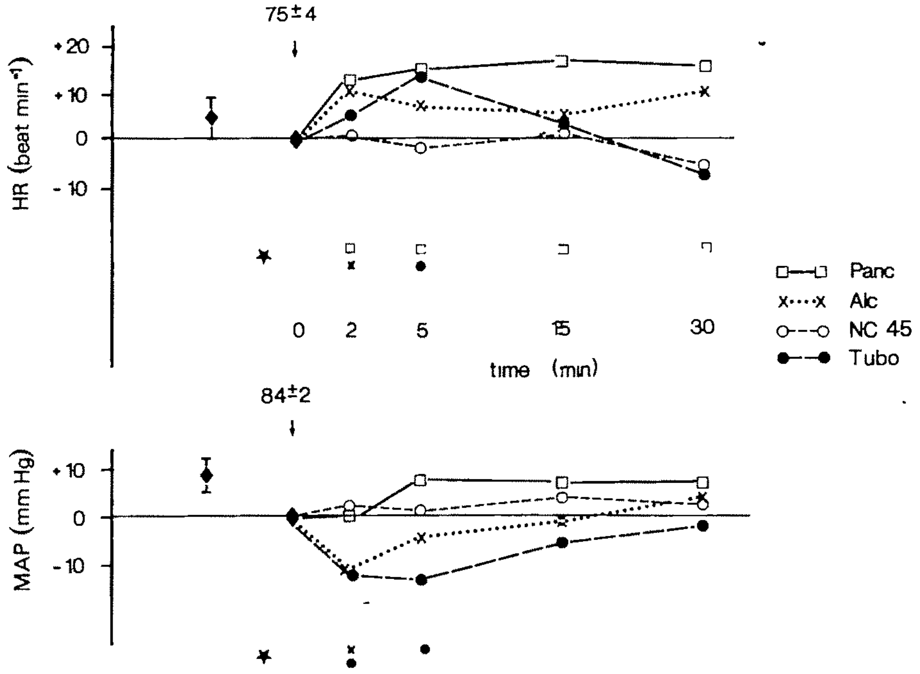

FIG. 2. Time-course of percent change in heart rate (HR) and mean arterial pressure (MAP) after bolus injections of relaxants (doses as in table III). ⧫ =value before induction of anaesthesia; ◆ =value immediately before injection of relaxant ↓. Significantly different changes are marked in line with * at the different times ($P<0.05$).

The short time-course of action of Org NC 45 seen in animals (Durant et al., 1979) and in man (Agoston et al., 1980; Crul, Krieg and Booij, 1980), is confirmed by our results. Katz (1971) reported a recovery time to 90% of control twitch tension of 58 min after a bolus of pancuronium 40 μg kg^{-1}, which is in agreement with our results (62 μg kg^{-1}, 73 min). Allowing for the different doses used, the duration of action of a bolus injection of Org NC 45 (degree of block averaging 83.8%) is only one-third that of an equipotent dose of pancuronium. The same is true for the duration of useful surgical relaxation (duration 25). After a bolus of pancuronium 40 μg kg^{-1} (Katz, 1971) or 62 μg kg^{-1} (this study) duration 25 was 26 or 34 min respectively. Again, pancuronium acted three times longer than Org NC 45. Thus the time course of action of Org NC 45 almost meets the demands of an "ideal short acting" non-depolarizing muscle relaxant (Savarese, and Kitz, 1975).

During maintenance of neuromuscular blockade (repeated administration of constant doses of relaxant at 25% recovery of twitch tension) pancuronium, alcuronium and tubocurarine showed clear evidence of cumulation; duration 25 was significantly prolonged after the second maintenance dose. In the case of Org NC 45 both duration 25 and % block were virtually unchanged until the fourth repeat injection (duration 25 ranging from 8.0 to 9.0 min and % block ranging from 87.1% to 90.2%. Agoston and others (1980) reported that maintenance doses during long-lasting operations were "required at a remarkably regular rate".

The absence of chronotropic or pressor effects after the administration of Org NC 45 is notable. In spite of the relatively inaccurate method of arterial pressure monitoring, the time course of changes in arterial pressure and heart rate are similar to those reported by other investigators (Kennedy and Kelman, 1970; Loh, 1970; Kelman and Kennedy, 1971; Coleman et al., 1972). Differences between these and our results are doubtless because of the greater accuracy of their methods or the different doses of relaxants used in some cases. Changes in heart rate and arterial pressure following intubation of the trachea are of minor importance in this study because in half of the patients suxamethonium had been given and the tracheal tube inserted 14–19 min before administration of the non-depolarizing relaxants, whereas in the others the tracheal tube was inserted not earlier than 4–12 min after injection of the non-depolarizing relaxant when the maximum twitch depression was reached. Moreover, there was no difference in heart rate and arterial pressure changes between these two groups. Any influence of premedication upon heart rate and arterial pressure was probably negligible because of the low dosage of these drugs and the time interval of at least 1 h between premedication and the administration of the relaxant. We conclude that Org NC 45, in the doses used, is free from vagolytic and cardio-depressive side-effects. It is a powerful neuromuscular blocking agent with a short duration of action and minimal cumulation of action. Further studies to determine its role in routine clinical anaesthesia are needed.

ACKNOWLEDGEMENT

We are grateful to the chairman of the division of Anesthetics, Dr P. Ponsioen, for his cooperation in organizing the clinical session.

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EFFICACITE RELATIVE D'ORG NC 45, DU PANCURONIUM, DE L'ALCURONIUM ET DE LA TUBOCURARINE CHEZ L'HOMME ANESTHESIE

RESUME

L'efficacité relative, la durée d'action et les effets cardiovasculaires d'Org NC 45, qui est un nouvel agent de blocage neuromusculaire non dépolarisant, ont été comparés aux facteurs correspondants du pancuronium, de l'alcuronium et de la tubocurarine sur 64 malades anesthésiés. Leur efficacité relative (ED_{50}) par rapport à Org NC 45 a été de 1,74, 3,69 et 8,57 respectivement. Administré à des doses entraînant une relaxation chirurgicale utile, la durée d'action d'Org NC 45 a été de 34%, 39% et 26% de celle du pancuronium, de l'alcuronium et de la tubocurarine. Après l'administration de doses répétées, n'a constaté aucune accumulation d'Org NC 45. Le nouveau médicament n'entraîne aucun effet sur la pression artérielle ou sur la fréquence cardiaque.

DIE RELATIVE STÄRKE VON ORG NC 45, PANCURONIUM, ALCURONIUM UND TUBOCURARIN IN NARKOTISIERTEN MENSCHEN

ZUSAMMENFASSUNG

Die relative Stärke, der zeitmässige Wirkungsablauf und die kardivaskulären Wirkungen von Org NC 45, eines neuen, nicht-depolarisierenden neuromuskulären Blockierungsmittels, wurden mit denen von Pancuronium, Alcuronium und Tubocurarin in 54 narkotisierten Menschen verglichen. Die relative Stärke (ED$_{50}$) dieser Drogen im Vergleich zu Org NC 45 war jeweils 1,74, 3,69 und 8,57. In Dosen, die eine wirkungsvolle chirurgische Entspannung bewirkten, betrug die Wirkungsdauer von Org NC 45 jeweils 34%, 39% und 26% von Pancuronium, Alcuronium und Tubocurarin. Nach Verabreichung wiederholter Dosen kam es bei Org NC 45 zu keiner Kumulierung, und die Droge war auch frei von allen Nebenwirkungen auf arteriellen Druck und Herztätigkeit.

POTENCIA RELATIVA DEL "ORG NC 45", PANCURONIUM, ALCURONIUM Y TUBOCURANINA EN EL HOMBRE ANESTESIADO

SUMARIO

Se ha comparado la potencia relativa, su acción en el transcurso del tiempo y los efectos cardiovasculares del Org NC 45, que es un neuvo agente de bloqueo neuromuscular no despolarizante, con las mismas características del pancuronium, alcuronium y de la tubocuranina en 64 pacientes anestesiados. La potencia relativa (ED$_{50}$) en comparación con el Org NC 45 fue de 1,74, 3,69, y de 8,57 respectivamente. La duración de la acción del Org NC 45, en dosis que ocasionaron una útil relajación quirúrjica, fue del 34%, 39% y del 26% de las correspondientes al pancuronium, alcuronium y a la tubocuranina. Después de administrar repetidas dosis no se apreció acumulación alguna por parte del Org NC 45. La nueva droga no ejerció efecto alguno en la presión arterial ni en el ritmo cardiaco.

Br. J. Anaesth. (1980), **52**, 789

FAZADINIUM PHARMACOKINETICS IN PATIENTS WITH LIVER DISEASE

P. DUVALDESTIN, J. SAADA, D. HENZEL AND G. SAUMON

SUMMARY

Serum concentrations of fazadinium were measured in eight patients with cirrhosis and eight patients with total biliary obstruction who underwent abdominal surgery. A biexponential decay of the concentration was observed after a single i.v. injection of fazadinium. A two-compartment open model was used in the pharmacokinetic analysis of the data. The pharmacokinetic parameters were compared with those obtained in 11 normal patients. A 90% increase in both the distribution half-life ($T_{\frac{1}{2}}^{\alpha}$), from 10 min to 19 min, and in the elimination half-life ($T_{\frac{1}{2}}^{\beta}$), from 82 min to 153 min, was observed in patients with cirrhosis. These changes are the consequence of an increase (60%) in the total apparent volume of distribution (*V*). In contrast, the plasma clearance (*Cl*) was not modified. Total biliary obstruction was associated with very little change in the pharmacokinetics of fazadinium, $T_{\frac{1}{2}}^{\beta}$ being slightly prolonged to 103 min. No significant decrease in plasma clearance was observed in patients with cholestasis. These results suggest that biliary excretion of fazadinium does not represent an important supplementary pathway to renal excretion. The relatively rapid decrease of the blood concentration of fazadinium compared with other non-depolarizing relaxants is probably related to another extrarenal pathway of elimination which has not yet been identified.

Non-depolarizing muscle relaxants are excreted mainly unchanged by the kidneys. Fazadinium is more rapidly eliminated from the body than other non-depolarizing relaxants despite its relatively small urinary excretion accounting for only 50% of the dose administered (Duvaldestin et al., 1979). It has been suggested, therefore, that biliary excretion may represent an important supplementary pathway of elimination for fazadinium in man. This is further supported by the minor pharmacokinetic alterations observed in patients with complete renal failure (Duvaldestin et al., 1979). The influence of two different types of liver disease, namely cirrhosis and extrahepatic cholestasis, on the pharmacokinetics of fazadinium was investigated in the present study.

METHODS

Eight patients with cirrhosis and eight patients with total biliary obstruction undergoing abdominal surgery were investigated during anaesthesia. The characteristics of the patients and the surgical procedures are listed in table I. At the time of surgery, none of the patients had clinical evidence of ascites or oedema. Liver function tests (table II) consisted of the measurement of total serum bilirubin and plasma protein concentrations, serum transaminase and alkaline phosphatase concentrations, and prothrombin time. Patients with cholestasis were treated with vitamin K_1 before surgery. None of the patients with liver disease had biological evidence of impairment of renal function. These patients were compared with a group of patients free from liver disease undergoing general anaesthesia for elective abdominal surgery, described in a previous report (Duvaldestin et al., 1979).

The same anaesthetic procedure was used for all patients. Premedication consisted of atropine 0.5 mg and droperidol 5–15 mg given i.m. or of diazepam 5–15 mg given orally. Anaesthesia was induced with thiopentone 5–7 mg kg^{-1} and maintained with 33% oxygen in a nitrous oxide mixture delivered by mechanical ventilation. Suxamethonium 0.8 mg kg^{-1} was given i.v. to facilitate tracheal intubation. Phenoperidine or fentanyl was given in repeated doses. Fazadinium was injected i.v. in a single dose of 1, 1.5 or 2 mg kg^{-1}, according to the duration of operation, which varied from 150 to 400 min. Serial blood samples were obtained from the 5th to the 360th min after injection of fazadinium. Urine samples were collected from patients with an indwelling catheter, 3, 6 and 24 h after administration of the drug. The concentration of fazadinium in serum or urine was measured fluorimetrically

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0007-0912/80/080789-06 $01.00

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TABLE I. *Details of patients studied. Patients* 1 *to* 8 *had cirrhosis and patients* 9 *to* 16 *had extrahepatic cholestasis.*
BSA= body surface area; Ca= carcinoma

Patient	Sex	Age (yr)	Weight (kg)	BSA (m^2)	Aetiology	Surgical procedure
1	F	42	56	1.55	Alcoholic	Portacaval shunt
2	F	51	53	1.50	Alcoholic	Portacaval shunt
3	M	50	62	1.67	Alcoholic	Portacaval shunt
4	M	61	76	1.92	Alcoholic	Splenorenal shunt
5	F	49	45	1.40	Alcoholic	Omentopexy
6	M	51	58	1.67	Alcoholic	Aorto–femoral prosthesis
7	F	58	46	1.49	Alcoholic	Abdominal herniae
8	F	51	59	1.57	Schistosomiasis	Splenorenal shunt
9	M	65	66	1.74	Ca pancreas	Biliary–intestinal bypass
10	M	57	70	1.79	Ca pancreas	Biliary–intestinal bypass
11	M	48	47	1.47	Ca pancreas	Biliary–intestinal bypass
12	F	65	45	1.44	Ca pancreas	Biliary–intestinal bypass
13	M	49	43	1.41	Ca pancreas	Laparotomy
14	M	48	66	1.74	Ampullary tumour	Pancreato–duodenal resection
15	M	63	63	1.73	Choledocolithiasis	Bile duct desobstruction
16	M	40	72	1.91	Choledocolithiasis	Bile duct desobstruction

TABLE II. *Serum concentrations of bilirubin, plasma transaminase and alkaline phosphatase concentrations and plasma protein and albumin concentrations of patients* (1 *to* 8) *with cirrhosis and* (9 *to* 16) *cholestasis.* †*Normal value* <30 *u. litre*$^{-1}$; ‡*normal value* <170 *u. litre*$^{-1}$

Patient	Total bilirubin (μmol litre^{-1})	Transaminase s.g.p.t.† (u. litre^{-1})	Alkaline phosphatase‡ (u. litre^{-1})	Prothrombin time (% of control)	Total proteins (g litre^{-1})	Albumin (g litre^{-1})
1	27	12	130	43	63	30.2
2	18	18	80	60	66	31.7
3	30	27	250	78	59	36
4	10	12	65	75	70	31.5
5	145	26	65	39	64	29.8
6	36	10	90	75	69	34.5
7	22	15	140	52	71	32
8	17	15	110	50	66	31.3
9	243	—	—	90	67	—
10	244	55	465	83	72	—
11	104	165	1200	75	67	—
12	156	300	900	100	66	34
13	240	16	160	80	62	28
14	274	93	700	80	63	27.1
15	154	200	875	100	69	36.2
16	236	210	750	90	68	40.8

(Pastorino, 1978). The pharmacokinetics of fazadinium were analysed according to a two-compartment open model described in detail in a previous report (Duvaldestin, Henzel et al., 1978). Pharmacokinetic parameters were computed using an identification algorithm (Richalet, Rault and Pouliquen, 1971) which minimizes an error criterion between the observed values and those obtained by simulation of a two-compartment open model. Two-tailed Student's *t* tests were used to evaluate the differences between the groups of patients.

RESULTS

The pharmacokinetic variables are presented in table III. A slower rate of disappearance of fazadinium from the plasma was observed in patients with liver disease (fig. 1). In patients with cirrhosis, both the distribution and elimination half-lives were

TABLE III. *Pharmacokinetic variables. Significantly different from the normal group:* $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.005$

	Normal group (mean ± SD) (n= 11)	Patients with cirrhosis (mean ± SD) (n= 8)	Patients with cholestasis (mean ± SD) (n= 8)
V_1 (litre kg^{-1})	0.133 ± 0.059	0.205 ± 0.062**	0.179 ± 0.069
V_2 (litre kg^{-1})	0.098 ± 0.043	0.150 ± 0.058*	0.141 ± 0.041*
k_{12} (h^{-1})	2.080 ± 1.53	2.070 ± 1.79	3.150 ± 1.76
k_{21} (h^{-1})	1.810 ± 0.58	1.261 ± 1.01	3.120 ± 2.85
k_{10} (h^{-1})	1.190 ± 0.51	0.590 ± 0.10***	0.940 ± 0.46

TABLE IV. *Serum half-lives of the distribution phase* ($T_{\frac{1}{2}}^{\alpha}$) *and elimination phase* ($T_{\frac{1}{2}}^{\beta}$), *total apparent volume of distribution* (V) *and plasma clearance* (Cl) *of fazadinium in* 11 *normal patients, eight patients with cirrhosis and eight patients with cholestasis. Value represent the mean* ± *SD. Significant differences compared with the normal group* $^{*}P<0.05$; $^{***}P<0.005$.

	Normal patients (n= 11)	Patients with cirrhosis (n= 8)	Patients with cholestasis (n= 8)
$T_{\frac{1}{2}}^{\alpha}$ (min)	10.2 ± 4.0	18.9 ± 13.3*	8.9 ± 6.02
$T_{\frac{1}{2}}^{\beta}$ (min)	82 ± 17	153 ± 55**	103 ± 25*
Cl (ml min^{-1} m^{-2})	96 ± 41	75 ± 16	82 ± 26
V (litre kg^{-1})	0.287 ± 0.110	0.448 ± 0.153***	0.350 ± 0.084

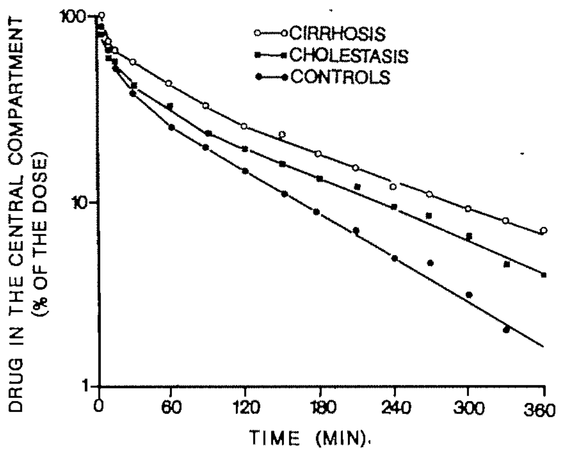

FIG. 1. Elimination of fazadinium from the central compartment in man after an i.v. injection. Semi-logarithmic plot of the amount of fazadinium present the central compartment (mean values) in 11 normal patients, eight patients with cirrhosis and eight patients with cholestasis.

prolonged (table IV). $T_{\frac{1}{2}}^{\alpha}$ and $T_{\frac{1}{2}}^{\beta}$ were increased by 90% from 10.2 to 18.9 min and from 82 to 153 min respectively. No significant increase in the plasma clearance of fazadinium was observed in patients with cirrhosis, whereas these patients exhibited a marked increase (56%) in the total apparent volume of distribution, from 0.287 to 0.448 litre kg^{-1}. The increase in both the central volume, V_1 and in the peripheral volume of distribution, V_2 (table III), contributed to the increase in V. Urinary excretion of fazadinium was diminished in patients with cirrhosis, 3, 6 and 24 h after its administration (table V).

In patients with cholestasis, only minor modifications of fazadinium pharmacokinetics were observed. $T_{\frac{1}{2}}^{\alpha}$ was not modified and $T_{\frac{1}{2}}^{\beta}$ was only slightly increased from 82 min to 103 min. The decrease of plasma clearance from 96 to 82 ml min^{-1} m^{-2} was not significant and was less pronounced than in patients with cirrhosis. V was not modified but V_2

TABLE V. *Cumulative urinary excretion of fazadinium and its metabolites calculated as the percentage of the injected dose* 3, 6 *and* 24 *h after injection to normal patients, patients with cirrhosis and patients with cholestasis. Values* (%) *represent the mean* ± *SEM, except for patients with cholestasis. Significantly different from the normal group* $^{*}P<0.05$; $^{**}P<0.01$

	Time after injection (h)		
	3	6	24
Normal group	34 ± 7 (n = 4)	45 ± 4 (n = 5)	50 ± 9 (n = 10)
Patients with cirrhosis	21 ± 8 (n = 7)	32 ± 8* (n = 7)	33 ± 12** (n = 8)
Patients with cholestasis			
Patient no. 12	23	30	35
Patient no. 14	32	40	57

was increased by about 40% (table III). In three patients with cholestasis the serum concentration of metabolites was also determined. The concentrations of metabolites never exceeded 3% of the total plasma concentration and were comparable to values observed in control patients (Duvaldestin et al., 1979).

DISCUSSION

Previous pharmacokinetic studies have suggested that a substantial fraction of the dose of fazadinium could be excreted by the liver. Compared with other non-depolarizing relaxants, fazadinium presents the following properties: (1) it disappears more rapidly from the plasma with an elimination half-life of 80 min instead of 120 min or more for other agents; (2) its cumulative urinary excretion accounts for only 50% of the dose, which is relatively similar to pancuronium excretion (Agoston et al., 1973). However, when urine was collected accurately via an indwelling catheter we found greater values averaging 65–70% of the dose of pancuronium administered for 24 h urinary excretion. Cumulative urinary excretion accounted for approximately 80% of the dose of alcuronium (Raaflaub and Frey, 1972) and gallamine (Agoston et al., 1978); (3) its pharmacokinetics are less altered by renal failure than is the case for tubocurarine and pancuronium (Duvaldestin et al., 1979). The weight of this evidence supports the hypothesis of an extrarenal pathway of elimination. The liver disposition of fazadinium consists of biotransformation or biliary excretion. Inactivation through splitting of fazadinium by microsomal azoreductase does not represent a substantial fraction of the dose of fazadinium present in plasma and urine in man (Duvaldestin et al., 1979).

Biliary excretion represents an accessory pathway of excretion for most non-depolarizing muscle relaxants. Approximately 10% of the dose is excreted in the bile in the case of alcuronium (Raaflaub and Frey, 1972), tubocurarine (Meijer et al., 1979) and pancuronium (Agoston et al., 1973). This percentage is even less for dimethyl-d-tubocurarine (Meijer et al., 1979) and negligible for gallamine (Agoston et al., 1978). Greater biliary excretion of fazadinium, accounting for 20–40% of the dose administered, was expected from previous studies. However, the results of the present study suggest that the role of the liver in the disposition of fazadinium is less important than anticipated.

In cirrhosis, prolongation of the elimination half-life is solely a result of increased volume of distribution. In these patients no significant change of plasma clearance was observed and the delayed urinary elimination can also be explained by an increase in *V*.

More surprising was the absence of important pharmacokinetic changes in patients with extrahepatic cholestasis. In all patients studied, obstruction of the common bile duct was complete but had little effect on the profile of decline of the blood concentration. Neither the elimination half-life nor the plasma clearance were modified significantly in these patients. The reasons for there being no decrease in clearance in patients with liver diseases of both parenchymal and ductal types remain unclear.

Renal excretion was not compensating for the absence of hepatic excretion in patients with cirrhosis. In patients with cholestasis, however, urine was sampled in only two patients and increased compensatory renal excretion remains a possible mechanism of rapid excretion. By comparison, the pharmacokinetic alterations observed for pancuronium are more pronounced, especially for patients with cholestasis in whom the elimination half-life was prolonged by 100% compared with normal patients (Somogyi, Shanks and Triggs, 1977). This change corresponded to a decrease of plasma clearance which cannot be attributed solely to a defect in biliary excretion, the latter accounting for only 10% of the elimination of pancuronium.

The pharmacokinetic alterations associated with liver cirrhosis are similar for fazadinium and pancuronium and correspond essentially to an increase in *V*, whereas the direct influence of liver failure is negligible as suggested by the minor decrease of pancuronium clearance (Duvaldestin, Agoston et al., 1978) and unchanged fazadinium clearance.

From the present study it is concluded that liver disease will have only little influence on the duration of action of fazadinium. The absence of prolongation of the elimination half-life in cholestatic patients argues against substantial excretion of fazadinium in the bile. Another extrarenal pathway of elimination, which has not yet been demonstrated, remains a possible mechanism for the rapid disappearance of fazadinium from the body.

ACKNOWLEDGEMENTS

We express our thanks to Dr Richard Edelstein for assistance in reviewing the manuscript and to Miss Murielle de Marez for secretarial help.

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PHARMACOCINETIQUE DU FAZADINIUM SUR DES MALADES SOUFFRANT DU FOIE

RESUME

On a mesuré les concentrations de fazadinium dans le sérum de huit malades souffrant d'une cirrhose et de huit autres souffrant d'une obstruction biliaire totale, après qu'ils aient subi une intervention chirurgicale à l'abdomen. On a observé un affaiblissement biexponential de la concentration après une seule injection intraveineuse de fazadinium. On a utilisé, pour l'analyse pharmacocinétique des données, un modèle ouvert à deux compartiments. Les paramètres pharmacocinétiques ont été comparés à ceux obtenus sur onze patients sains. Une augmentation de 90% de la demi-vie de répartition ($T_{\frac{1}{2}}^{\alpha}$)—de 10 à 19 min—et de la demi-vie d'élimination ($T_{\frac{1}{2}}^{\beta}$)—de 82 à 153 min—a été observée sur les malades souffrant de cirrhose. Ces variations sont la conséquence d'une augmentation (60%) du volume apparent total de répartition (*V*). Par contraste, le coefficient d'épuration plasmatique (*Cl*) n'a pas été modifié. L'obstruction biliaire totale n'a été associé qu'à peu de changements dans la pharmacocinétique du fazadinium, $T_{\frac{1}{2}}^{\beta}$ étant légèrement prolongée jusqu'à 103 min. On n'a observé aucune diminution significative du coefficient d'épuration plasmatique sur les patients souffrant de cholestase. Ces résultats laissent penser que l'excrétion biliaire de fazadinium ne représente pas une voie supplémentaire importante d'excrétion rénale. La diminution relativement rapide des concentrations de fazadinium dans le sang—par comparaison à d'autres décontracturants non dépolarisants—est probablement liée à une autre voie d'élimination extra-rénale que l'on n'a pas encore identifiée.

PHARMAKOKINETISCHE WIRKUNGEN VON FAZADINIUM BEI PATIENTEN MIT LEBERKRANKHEITEN

ZUSAMMENFASSUNG

Fazadinium-Serumkonzentrationen wurden bei acht Patienten mit Leberzirrhose, und bei acht Patienten mit Gallengangverstopfung gemessen, die alle Unterleibsoperationen unterzogen wurden. Ein Biexponentialzerfall der Konzentration wurde nach einer intravenosen Einzelinjektion von Fazadinium beobachtet. In der pharmakokinetischen Datenanalyse wurde ein zeiteiliges offenes Modell verwendet. Die pharmakokinetischen Parameter wurden mit denen von 11 normalen Patienten verglichen. Ein 90%iger Anstieg sowohl in der Verteilungs-Halbwertzeit ($T_{\frac{1}{2}}^{\alpha}$), von 10 auf 19 min, und in der Eliminierungs-Halbwertzeit ($T_{\frac{1}{2}}^{\beta}$), von 82 auf 153 min wurde in den Zirrhose-Patienten beobachtet. Diese Veränderungen sind die Folge eines 60%igen Anstieges im totalen Verteilungsvolumen (*V*). Im Gegensatz dazu war die Plasmaklärung (*Cl*) nicht modifiziert. Die totale Gallengangverstopfung ergab sehr wenig Veränderung in den pharmakokinetischen Effekten von Fazadinium—$T_{\frac{1}{2}}^{\beta}$ war etwas verlangert auf 103 min. Kein wesentliches Absinken von *Cl* wurde bei Patienten mit Cholestase beobachtet. Diese Resultate zeigen, dass die Gallenausscheidung von Fazadinium keinen zusätzlichen Nierenausscheidungsweg darstellt. Das relativ schnelle Absinken der Blutkonzentration von Fazadinium verglichen mit anderen nicht-depolarisierenden Entspannungsmitteln beruht wahrscheinlich auf einem anderen extrarenalen Ausscheidungsweg, der noch nicht identifiziert wurde.

FÀRMACOCINETICAS DEL FAZADINIUM EN PACIENTES CON ENFERNEDADES DE HIGADO

SUMARIO

Se midieron concentraciones de suero de fazadinium en 8 pacientes con cirrosis y en otros 8 con obstrucción bilial total, quienes sufrieron cirgugía abdominal. Se observó una caída biexponencial después de una sóla inyección intravenosa de fazadinium. En el análisis farmacocinético de los datos se usó un modelo abierto de dos compartimentos. Los parámetros farmacocinéticos se compararon con los obtenidos en 11 pacientes normales. En aquellos pacientes con cirrosis se observó un incremento del 90% tanto en la mitad del periodo de vida de la distribución ($T_{\frac{1}{2}}^{\alpha}$), desde 10 a 19 minutos, como en la mitad del periodo de vida de la eliminación ($T_{\frac{1}{2}}^{\beta}$), desde 82 a 153 minutos. Estos cambios fueron consecuencia de un incremento (60%) en el volumen total aparente de la distribución (*V*). Por el contrario, la eliminación del plasma (*Cl*) no sufrió modificación alguna. La obstrucción bilial total se asoció con un cambio muy pequeño en las farmacocinéticas del fazadinium,

prolongándose ligeramente $T_{\frac{1}{2}}^{\beta}$ hasta 103 minutos. No se observó disminución significativa en la eliminación del plasma en aquellos pacientes con colestasis. Estos resultados sugieren que la excreción bilial del fazadinium no representa una ruta suplementatia importante para la excreción renal. La disminución, relativamente rápida, de la concentración de fazadinium en la sangre, en comparación con otros relajantes no despolarizantes, queda probalemente relacionada con otra ruta extra renal de eliminación que no ha sido aún identificada.

Br. J. Anaesth. (1980) **52**, 795

PHARMACOKINETICS OF HIGH-DOSE FENTANYL

A study in patients undergoing cardiac surgery

J. G. BOVILL AND P. S. SEBEL

SUMMARY

The pharmacokinetics following a bolus injection of fentanyl 60 $\mu g\ kg^{-1}$ as the sole anaesthetic in five patients undergoing cardiac surgery are described. Before cardiopulmonary bypass the kinetics can be described by a biexponential decay curve with an initial half-life of 1.7 ± 0.85 min and a half-life during the tissue uptake phase of 69 ± 8.2 min. Two patients had secondary peaks in plasma fentanyl concentration during the first 5 min after injection. After 5 min cardiopulmonary bypass with haemodilution, the fentanyl concentration decreased by an average of 53%. The half-life in the post-bypass elimination phase was 423 ± 36.9 min. No second peaks during the elimination phase were found.

Information about the pharmacokinetics of fentanyl has, until recently, been limited by lack of any assay method suitable for measuring small concentrations of the drug in plasma. In addition, the original assay method (Hess, Herz and Friedel, 1971) required administration of tritiated fentanyl which, for ethical reasons, precluded studies in man. Recently, however, a sensitive and specific radioimmunoassay capable of measuring concentrations less than 1 ng of fentanyl in plasma has been developed (Henderson et al., 1975; Michiels, Hendriks and Heykants, 1977). This method has been used by Schleimer and others (1978) to describe the pharmacokinetics of fentanyl in subjects receiving doses of up to 1.0 $mg\ m^{-2}$ (approx. 30 $\mu g\ kg^{-1}$), and more recently by Lunn and others (1979) who gave doses of fentanyl 75 $\mu g\ kg^{-1}$ as an infusion followed by a bolus injection.

In clinical practice, Becker and others (1976) reported biphasic respiratory depression after fentanyl and Adams and Pybus (1978) reported three cases of delayed respiratory depression which they attributed to fentanyl. Secondary peaks in plasma fentanyl concentrations have been reported by McQuay and others (1979) and by Stoekel, Hengstmann and Schüttler (1979) during the elimination phase. The latter authors found that 16% of the administered dose was contained in the stomach wall 10 min after injection. They suggested that entero–systemic recirculation might account for the observed secondary peaks and explain the occurrence of delayed respiratory depression.

The purpose of this study was to investigate the pharmacokinetics of bolus injection of fentanyl 60 $\mu g\ kg^{-1}$, used as the sole anaesthetic in patients undergoing cardiac surgery.

METHODS

Five patients undergoing elective cardiac surgery with cardiopulmonary bypass were studied. Three of these undergoing coronary artery bypass grafts were receiving beta-blocking drugs and nitrates for the control of angina pectoris, one patient received methyldopa for the control of hypertension and another received disopyramide for the control of arrhythmias. Beta-blocking drugs were discontinued 24 h before surgery. Two patients undergoing valve replacement operations were taking digoxin and diuretics for the control of congestive heart failure. In all patients the results of laboratory tests of renal and hepatic function were within normal limits. Details of the patients and type of operation are shown in table I.

The conduct of anaesthesia followed the authors' normal practice. Premedication was lorazepam 5 mg orally, 1.5 h before surgery. A radial artery cannula and a wide-bore central venous catheter inserted via the external jugular vein served for circulatory monitoring and blood sampling. Anaesthesia was induced with fentanyl 60 $\mu g\ kg^{-1}$ injected i.v. over a 2-min period, followed by pancuronium 8 mg for neuromuscular blockade. Ventilation of the lungs was

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0007-0912/80/080795-07 $01.00

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TABLE I. *Details of patients and operations. CPB= cardiopulmonary bypass*

Patient	Age (yr)	Sex	Wt. (kg)	Operation	Duration of CPB (min)
A	57	M	87	Coronary artery bypass grafts (2)	62
B	65	F	67	Aortic and mitral valve replacement, coronary artery bypass grafts (1)	133
C	45	F	53	Aortic and mitral valve replacement, tricuspid ring	183
D	52	M	79	Coronary artery bypass grafts (2)	83
E	64	M	70	Coronary artery bypass grafts (3)	87

assisted and then controlled manually using a facemask and 50% nitrous oxide in oxygen. Five minutes after induction the trachea was intubated and thermocouple probes inserted to the oesphagus, nasopharynx and triceps muscle to monitor body temperature. The bladder was catheterized. During anaesthesia ventilation was adjusted to maintain end-tidal carbon dioxide concentration in the range 4.5–5%. An arterial blood sample was taken within 30 min of induction for blood-gas analysis and served as a further check on the adequacy of ventilation.

Cardiopulmonary bypass was conducted using a Polystan Rygg–Kyvsgaard 5000 bubble oxygenator with moderate hypothermia (25 °C) and haemodilution to a haematocrit of 20–25%. Pump flow was maintained at 50–55 ml kg^{-1} min^{-1}. The carbon dioxide concentration in the expiratory vent of the oxygenator was kept constant at 6%, corresponding to Pa_{CO_2} 6 kPa.

Venous blood was sampled at 1, 2, 3, 4, 5, 10, 15 and 30 min after the end of injection and every 30 min thereafter until the end of surgery. In addition a sample was collected 5 min after the start of bypass. Sampling in the period after operation was at 3-h intervals until 24 h after the induction of anaesthesia. The urine production during each 1-h period after induction (3-h in the period after operation) was noted, the urine was well mixed and a 10-ml sample collected.

Plasma was separated from blood samples and all samples stored at −26 °C, until analysed. Fentanyl concentrations were determined in duplicate by radioimmunoassay (Michiels, Hendriks and Heykants, 1977). The coefficient of variation of the assay was 5% for a concentration of 1 ng ml^{-1} and 15% for concentrations greater than 10 ng ml^{-1}. The data were analysed by the "Method of Residuals" using a Hewlett–Packard 97 calculator programmed for the method of least squares. Statistical comparisons were made using Student's t test. Data are presented as mean values ± SEM.

RESULTS

The plasma concentration of fentanyl 1 min after injection showed considerable variation between patients, with a range from 31.2 to 200 ng ml^{-1} (mean 102.4 ± 36.48). By 2 min after injection 97% of the administered dose had disappeared from the plasma. In three patients (A, B and C) the decay curve until the onset of cardiopulmonary bypass could be described by a biexponential equation of the form $C = Ae^{-\alpha t} + Be^{-\beta t}$, with a rapid initial decline and a prolonged second phase (fig. 1). In the remaining two patients (D and E), after an initial decline a secondary peak occured between 3 and 5 min with increase in fentanyl concentrations of 13.5% and 31% respectively (fig. 2). This corresponded to the re-entry to the plasma compartment of fentanyl 23 µg and 14 µg respectively.

The presence of a secondary peak precluded the fitting of a biexponential curve to the data from the

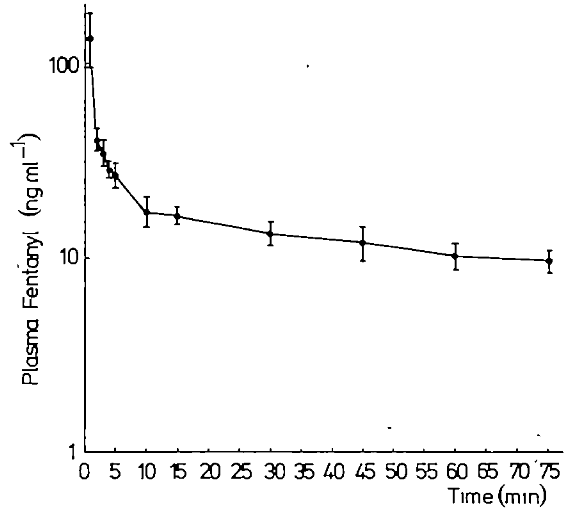

FIG. 1. Change in plasma fentanyl concentration (ng ml^{-1}) in the period before cardiopulmonary bypass (patients A, B and C) (mean ± SEM).

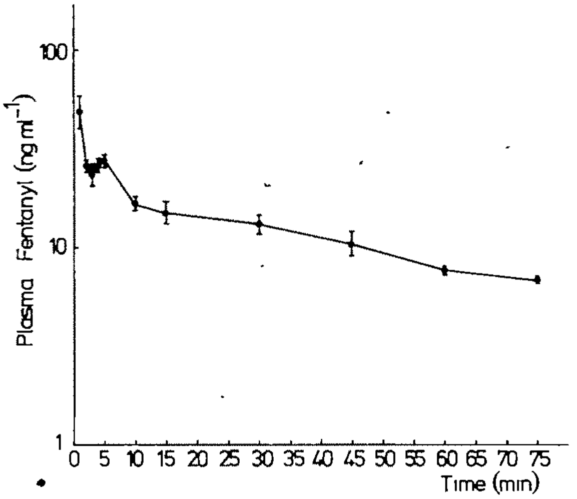

FIG. 2. Change in plasma fentanyl concentration (ng ml^{-1}) in the period before cardiopulmonary bypass (patients D and E) (mean ± SEM).

TABLE II. *Rate constants and half-lives for individual patients in the period until start of cardiopulmonary bypass.* $^*r = [\sum(obs)^2 - \sum(div)^2]/\sum(obs)^2$; $^\dagger r$ = *correlation coefficient for the linear regression equation* $\log C = \log B - \beta t$

Patient	α (min^{-1})	$T_{\frac{1}{2}}{}^{\alpha}$ (min)	β (min^{-1})	$T_{\frac{1}{2}}{}^{\beta}$ (min)	r
A	−0.2020	3.43	−0.00726	95.5	0.9988*
B	−0.7285	0.95	−0.00971	71.4	0.9611*
C	−0.8803	0.79	−0.00972	71.3	0.9423*
D			−0.01109	62.5	0.9662†
E			−0.01555	44.6	0.9678†
Mean	−0.6036	1.72	−0.01067	69.0	
SEM	0.2055	0.855	0.001370	8.22	

latter group, but the plasma concentrations during the second phase declined exponentially in a manner similar to that seen in the first group. The calculated parameters for both groups of patients are shown in table II.

There was a highly significant decrease of 53% ($P < 0.005$) in plasma concentrations within 5 min of the start of cardiopulmonary bypass. The reduction in plasma concentrations was greater than would have been expected from haemodilution alone (average decrease in haematocrit 41%), and corresponds to fentanyl 8 ± 0.8 μg being redistributed to the tissue during the first 5 min of bypass. At this time the blood and oesophageal temperature had decreased to 25 °C in all patients and the mean muscle temperature was 28 ± 3.6 °C. There was no obvious relationship between the temperature changes and the quantity of fentanyl leaving the plasma compartment.

There was no consistent pattern observed during this period. The increase in concentration seen in patients B and D during the last 30 min of bypass coincided with the marked diuresis during this period of 310 ml and 400 ml respectively. The change in plasma concentration during cardiopulmonary bypass is shown in figure 3.

Plasma concentrations showed no significant change in the first 2 h following bypass, but thereafter declined exponentially with a mean half-life of 423 ± 36.0 min (fig. 4, table III).

The urinary excretion of fentanyl was small—the mean percentage of the original dose excreted up to 24 h was 2.1 ± 0.42%. Urinary excretion rates

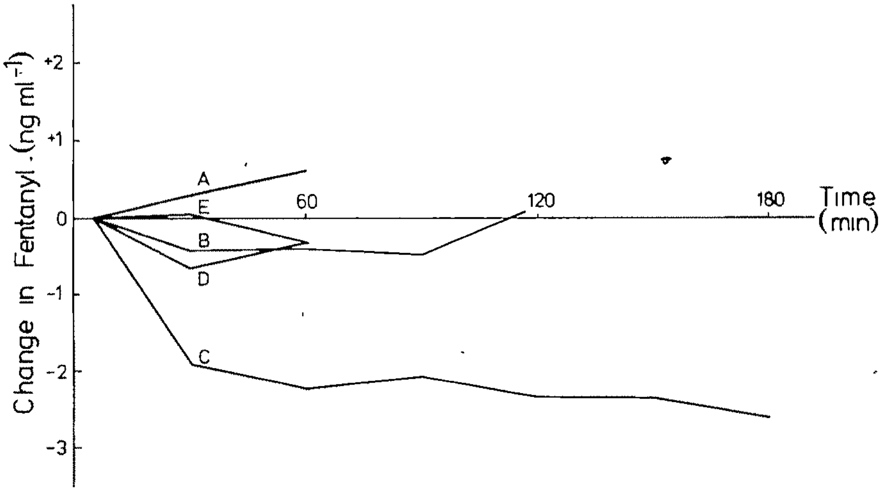

FIG. 3. Individual changes in plasma fentanyl concentrations (ng ml^{-1}) during cardiopulmonary bypass. Changes are measured from the concentration at the start of bypass.

TABLE III. *Rate constants and half-lives for individual patients in the period after cardiopulmonary bypass, calculated from the plasma fentanyl decay curves (plasma elimination) and from the urinary excretion rates of fentanyl calculated by the Sigma-Minus method (renal elimination).* r = *correlation coefficient for linear regression.*

	Plasma elimination			Renal elimination		
Patient	γ (min^{-1})	$T_{\frac{1}{2}}\gamma$ (min)	r	π (min^{-1})	$T_{\frac{1}{2}}\pi$ (min)	r
A	−0.00164	423	0.9472	−0.00129	538	0.9942
B	−0.00148	470	0.9819	−0.00238	291	0.9812
C	−0.00225	308	0.9905	−0.00265	261	0.9909
D	−0.00137	507	0.9812	−0.00203	342	0.9948
E	−0.00137	505	0.9397	−0.00207	335	0.9957
Mean	−0.00162	423		−0.00208	354	
SEM	0.000165	36.9		0.000228	48.5	

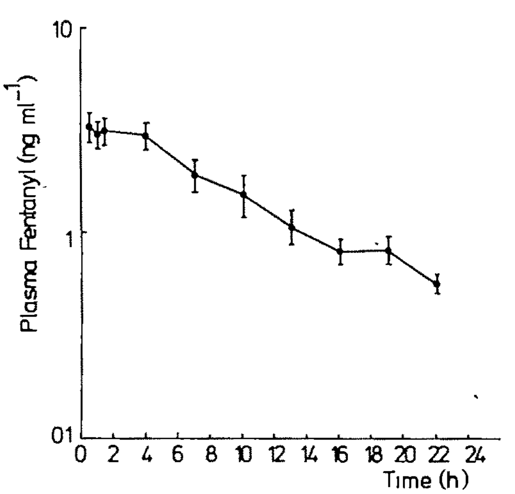

FIG. 4. Change in plasma fentanyl concentration (ng ml^{-1}) from the end of cardiopulmonary bypass until the following morning (mean ± SEM).

were variable, but tended to reflect rate of urine production (fig. 5).

Analysis of the urine excretion rate, using the Sigma-Minus method (Wagner, 1975), gave a mean elimination half-life of 354 ± 48.5 min, which was not significantly different from that calculated from the plasma concentrations ($t = 1.5$, $P > 0.05$).

DISCUSSION

The changes in plasma fentanyl concentrations in this study are in broad agreement with Lunn and others (1979) who studied a similar group of patients. Although they gave a larger dose (75 μg kg^{-1}) than ours it was infused over 5–8 min to 50 μg kg^{-1}, followed after 10–15 min by a bolus of 25 μg kg^{-1}. This difference in administration explains the smaller peak plasma fentanyl concentrations found by them.

The initial decline in plasma fentanyl concentration following bolus injection is rapid, with 95–98% of the administered dose disappearing from the plasma within 5 min (Michiels, Hendriks and Heykants, 1977; Murphy, Olson and Hug, 1979). The mean concentration at 1 min in a series of patients given 1 mg m^{-2} (30 μg kg^{-1}) by Schleimer and others (1978) was 228 ng ml^{-1}, which is considerably greater than the mean in this series (102 ± 36.5 ng ml^{-1}). However, there was considerable variation in the measured concentrations at 1 min in our series, and it is possible that in those patients with low initial values, the peak concentration had been reached before the 1-min sample was taken. Since we gave the fentanyl over a 2-min period and not as a true bolus, such a variation is to be expected.

Previous studies have shown that the plasma elimination of fentanyl can be described by a three-term exponential equation compatible with a three-compartment open pharmacokinetic model (Hull and McLeod, 1976; Schleimer et al., 1978; Murphy, Olson and Hug, 1979), although not all investigators have found such a pattern (McQuay et al., 1979; Stoeckel, Hengstmann and Schüttler, 1979). In this study plasma decay in three patients, up to the onset of cardiopulmonary bypass, could be described by a biexponential curve of the form $C = Ae^{-\alpha t} + Be^{-\beta t}$. In these patients the initial rapid phase had a mean half-life of 1.7 ± 0.85 min, which is within the range reported in other studies. During the second tissue uptake phase Murphy, Olson and Hug (1979) found a mean half-life of 30 min when dogs were given fentanyl 100 μg kg^{-1}. Schleimer and others (1978) reported half-lives in man which varied

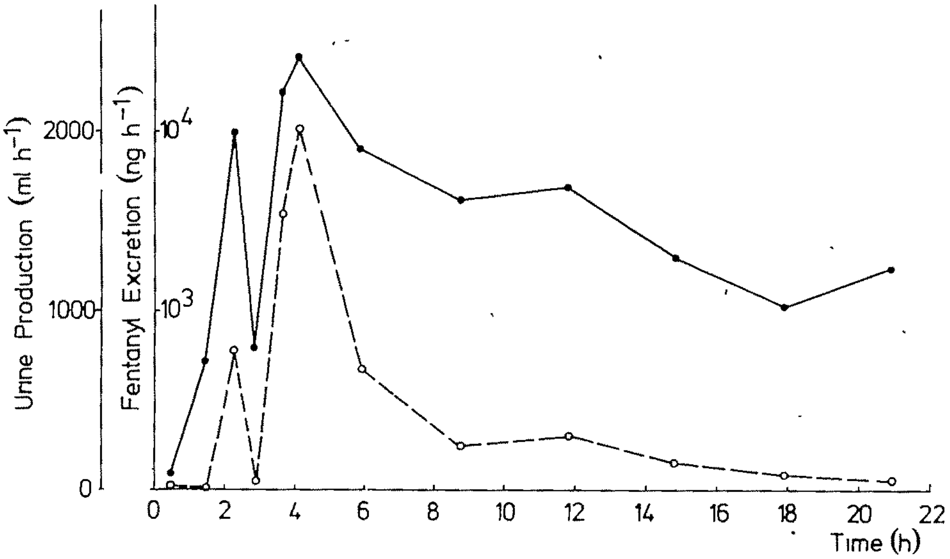

FIG. 5. Changes in the urinary excretion of fentanyl (ng h^{-1}) compared with the urine production rate (ml h^{-1}) in patient D from induction of anaesthesia until the following morning. Fentanyl excretion rate ● —— ●; urine production rate ○ - - - - ○.

between 5 and 21 min. The mean half-life in this report was 69 ± 8.2 min, which is considerably longer than in either of these two studies. Although the arbitrary division of the decay curve in the period before bypass fitted the data, it is possible that part of the terminal elimination phase may have been included in the calculation of second phase parameters and account for the discrepancy between our findings and those of other workers. Support for this hypothesis comes from the data presented by Ainslie, Eisele and Corkill (1979) who also arbitrarily partitioned their plasma concentration data, up to 120 min, into two compartments and reported a slow phase half-life of 89 ± 14 min.

The mean plasma half-life in the post-bypass elimination phase (423 ± 36.9 min) was also longer than other published findings which range from 170 to 356 min (Hull and McLeod, 1976; Michiels, Hendriks and Heykants, 1977; Schleimer et al., 1978; Murphy, Olson and Hug, 1979). This difference is perhaps to be expected when the patients in this study are compared with subjects normally included in pharmacokinetic investigations—healthy young adults. The average age of our patients was 65 yr and all had severe cardiovascular disease. It is known that, with advancing age, the rates of drug metabolism and excretion decrease (Grove, Toseland and Trounce, 1974; Crooks, O'Malley and Stevenson, 1976). In addition the effects of fasting before operation and the moderate under-hydration in the pre-bypass phase of surgery, followed by considerable haemodilution and fluid overload during and after cardiopulmonary bypass are all likely to distort drug kinetics, as are fluid shifts between body compartments associated with profound changes in body temperature.

The secondary peaks in fentanyl concentrations observed in two patients between 3 and 5 min were unexpected and difficult to explain. Secondary peaks occuring between 20 and 90 min following bolus injection of fentanyl have been reported by McQuay and others (1979) and Stoeckel, Hengstmann and Schüttler (1979), although no peaks were observed in any of our patients at these times. The second group of authors have suggested entero–systemic recirculation as a possible explanation for this phenomenon and have shown significant uptake of fentanyl by the stomach wall within a short time of injection. It is unlikely, however, that such an explanation could account for the much earlier peaks in our patients.

McQuay and others (1979) gave fentanyl 25 μg kg^{-1} during thiopentone–nitrous oxide–oxygen anaesthesia for major gynaecological surgery and observed significant secondary peaks occuring within 45 min of the end of surgery. They attributed this to the increased muscle tone and voluntary movement associated with the return of conciousness.

Considerable quantities of fentanyl are taken up from the plasma by skeletal muscle, with peak concentrations being reached within 5 min of injection (Hess, Herz and Friedel, 1971). Muscle rigidity is a well-recognized phenomenon following the rapid injection of fentanyl and it is possible that the occurrence of such rigidity before the onset of full myoneural block could release sufficient fentanyl from the skeletal stores to account for the observed secondary peaks. Considerable amounts of fentanyl are also taken up by the lungs (24% of the dose at 0.5 min) and it is likely that this organ has an important depot function for the redistribution of the drug for 5–10 min after administration (Hess, Herz and Friedel, 1971). During manual ventilation any decrease in compliance caused by chest wall rigidity would result in increased inflation pressure and thus intrapulmonary pressure. It is feasible that this could be sufficient to disturb the pharmacokinetic equilibrium within the lungs and cause sufficient redistribution of fentanyl into the central compartment to account for the observed secondary peaks in patients D and E.

The reduction in plasma fentanyl concentration at the start of cardiopulmonary bypass was greater than could have been expected from haemodilution alone; considerable amounts of the drug were redistributed to the tissues at this time. The onset of cardiopulmonary bypass is associated with profound physiological changes—haemodilution, hypothermia and large increases in circulating catecholamines (Stanley et al., 1979) and it is therefore not surprising that the pharmacokinetic equilibrium was disturbed. It is not possible, from the results of this study, to say which individual factors might be responsible for this disturbance. Indeed, surprisingly little is known about pharmacokinetics during cardiopulmonary bypass, and there is considerable scope for further research.

The excretion of unchanged fentanyl in the urine plays a minor part in elimination (Hess, Stiebler and Herz, 1972). Schleimer and others (1978) found that 14–21% of the given dose was excreted at 50 h. Murphy, Olson and Hug (1979) found that, in dogs, only $4 \pm 0.9\%$ of the administered dose was excreted within 6 h. The average percentage of the administered dose excreted by our patients up to 24 h ($2.1 \pm 0.42\%$) was considerably less than either of these. Following cardiac surgery with cardiopulmonary bypass, patients often have a diminished cardiac output with reduced renal blood flow, and urine production. All the patients in this series needed diuretics in the period after operation to maintain adequate urine flow. It is not unexpected that the renal excretion of fentanyl was less than that in healthy subjects. Reduced tissue perfusion associated with a low cardiac output would also prolong the elimination phase.

The mean plasma fentanyl concentrations remained greater than 1 ng ml^{-1} until 14 h after injection (fig. 4), but it should be emphasized that the concentration was still greater than this in two patients at 24 h. A concentration of 1 ng ml^{-1} has been suggested as the threshold for respiratory depression in dogs anaesthetized with enflurane (Hug and Murphy, 1979), although the threshold in the anaesthetized human is likely to be greater. It is our practice to ventilate the patient's lungs overnight and a persisting concentration of fentanyl sufficient to maintain respiratory depression is an advantage. In all five patients the tracheal tube was removed without difficulty within 24–26 h after fentanyl. However, the possibility that significant plasma concentrations of fentanyl may remain for 24 h following the use of "high-dose" fentanyl techniques must be borne in mind; we would emphasize that this technique should only be used where facilities exist for artificial ventilation after surgery.

ACKNOWLEDGEMENTS

We would like to thank Dr J. Heykants and Professor W. Soudijn for their help in the preparation of the experimental programme and advice on the manuscript. We would also like to thank Mr Ivo Gevens, Department of Drug Metabolism and Pharmacokinetics, Janssen Pharmaceutica, Belgium, for performing the assays and the nurses on our Intensive Care Unit for their help.

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PHARMACOCINETIQUE DU FENTANYL ADMINISTRE EN FORTES DOSES

Etude effectuée sur des malades subissant une intervention chirurgicale au coeur

RESUME

On décrit dans cet article la pharmacocinétique obtenue après une injection de fentanyl à raison de 60 μg kg^{-1}, celui-ci étant le seul agent anesthésiant utilisé sur cinq malades subissant une intervention chirurgicale au coeur. Avant le pontage cardiopulmonaire, on peut décrire la cinétique à l'aide d'une courbe bi-exponentielle allant en s'affaiblissant ou la demi-vie initiale est de 1,7±0,85 min et où la demi-vie pendant la phase de fixation dans les tissus est de 69±8,2 min. Deux malades ont eu des crêtes secondaires sans les concentrations de fentanyl dans le plasma au cours des 5 premières minutes qui ont suivi l'injection. Après 5 min de pontage cardiopulmonaire, à l'aide d'une hémodilution, la concentration de fentanyl a baissé d'une moyenne de 53%. La demi-vie au cours de la phase d'élimination qui a suivi le pontage a été de 423±36,9 min. On n'a constaté aucune crête secondaire pendant la phase d'élimination.

DIE PHARMAKOKINESE VON FENTANYL IN HOHEN DOSEN

Eine Studie an Patienten bei Herzoperationen

ZUSAMMENFASSUNG

Die Pharmakokinese nach Bolusinjektionen von Fentanyl 60 μg kg^{-1} als einzigem Narkosemittel bei 5 Patienten für Herzoperationen wird beschrieben. Vor dem Herz-Lungen-Bypass können die kinetischen Verhältnisse durch eine biexponentielle Zerfallskurve mit einer anfänglichen Halbwertszeit von 1,7±0,85 min beschrieben werden, mit einer Halbwertszeit während der Gewebeaufnahmephase von 69±8,2 min. Zwei Patienten zeigten sekundäre Spitzenwerte der Fentanyl-Plasmakonzentration während der ersten 5 min, nach der Injektion. Nach fünfminütigem Herz-Lungen-Bypass mit Hämodilution sank die Fentanylkonzentration um durchschnittlich 53%. Die Halbwertzeit in der Postbypass-Eliminierungsphase betrug 423±36,9 min. Wahrend dieser Phase kam es zu keinen weiteren Spitzenwerten.

FARMACOCINETICAS DE ALTAS DOSIS DE FENTANIL

Un estudio sobre pacientes que están sufriendo cirugía cardíaca

SUMARIO

Se describen las farmacocinéticas que siguen a una inyección de 60 μg kg^{-1} de fentanil, a modo de anestésico único, en cinco pacientes que están sufriendo cirugía cardíaca. Antes de la desviación cardiopulmonar, las cinéticas pueden describirse mediante uma curva descendente bi-exponencial con una media vida inicial de 1,7±0,85 min y una media vida de 69±8,2 min durante la fase de adaptación del tejido. Dos de los pacientes presentaron crestas secundarias en la concentración de plasma de fentanil, durante las primeros cinco minutos que siguieron a la inyección. Después de una desviación cardiopulmonar de 5 minutos, con hemodilución, la concentración de fentanil disminuyó en un promedio del 53%. La media vida en la fase de eliminación de la posdesviación fue de 423±36,9 min. No se apreciaron segundas crestas durante la fase de eliminación.

Br. J. Anaesth. (1980), **52**, 803

INDUCTION OF ANAESTHESIA WITH ETOMIDATE: HAEMODYNAMIC STUDY OF 36 PATIENTS

A. Criado, J. Maseda, E. Navarro, A. Escarpa and F. Avello

SUMMARY

The haemodynamic effects of anaesthetic induction with i.v. etomidate have been assessed in 36 patients. The variables studied were recorded under basal conditions and 3 and 10 min after induction, before surgical stimulus. There was a reduction in cardiac output, stroke volume and arterial pressure, and a compensating increase in heart rate. Pulmonary arterial pressure and vascular resistance, central venous pressure and pulmonary capillary wedge pressure were virtually unchanged. Although etomidate has a negative inotropic effect, the variables which were depressed remained at all times within acceptable limits.

Reneman and others (1975) demonstrated experimentally in dogs that i.v. administration of etomidate 1.5 mg kg^{-1} produced a slight decrease of the aortic pressure. At a dose of 2.5 mg kg^{-1}, this was associated with an increase of the heart rate. Weymar and others (1974), using doses in the range 0.2–1.6 mg kg^{-1}, observed a decrease in mean aortic pressure attributable to reduction of peripheral resistance, and an increase in cardiac output because of an increase in heart rate.

Bruckner and others (1974), Hempelman and others (1974), and Kettler and Sonntag (1974) also assessed the haemodynamic effects of the drug in anaesthetized patients, but the numbers studied were small (seven, nine and five patients respectively), and the results were not exclusively attributable to etomidate; other agents were given and the patients' circulatory state was not stable.

We have assessed the haemodynamic changes following i.v. administration of etomidate used as the sole anaesthetic.

PATIENTS AND METHODS

Anaesthesia was induced with etomidate in 36 patients (18 males and 18 females) who had received no premedication and were undergoing elective abdominal, orthopaedic or thoracic surgery. All the patients had been informed of the nature of the study and had given consent. The mean age was 50.6 yr (±SD 16.5), mean body weight 66.9 kg (±10.6), mean height 164 cm (±7 cm), and mean body surface area was 1.72 m^2 (±0.14). The dose of etomidate (0.45 mg kg^{-1}) was administered over a constant time of 60 s via a peripheral vein.

A Waters MR-105 Record System (Waters Company, Rochester, Minn., U.S.A.) was used for data collection. Cardiac output (CO) was measured by the dye dilution technique with indocyanine green (Cardio-Green), with a Medicut Argyle No. 8 cannula inserted into a radial artery, after performing Allen's test (Allen, 1929). A Swan–Ganz 7F three-way catheter was inserted via an antecubital vein and advanced until its tip was located in the pulmonary artery. The measurement of the cardiac output from the dye dilution curve was carried out following Hamilton's procedure of exponential extrapolation of the curve on semi-logarithmic graph paper (Kinsman, Moore and Hamilton, 1929; Guyton, Jones and Coleman, 1973).

Heart rate was obtained by continuous recording of the e.c.g. (HR); arterial pressure (BP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCP) and central venous pressure (CVP) were measured using conventional transducers.

Cardiac index (CI), stroke volume (SV), pulmonary (PR) and peripheral (PeR) resistances and left ventricular work (LVW) were calculated (Yang et al., 1974).

All variables were recorded under basal conditions with the patient awake, and again 3 and 10 min after induction with etomidate, before any surgical stimulus.

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0007-0912/80/086803-04 $01.00

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TABLE I. *Haemodynamic measurements during induction of anaesthesia with etomidate (mean and SD).* * *$P < 0.05$ compared with basal values*

	Basal	3 min	10 min
Cardiac output (litre min^{-1})	5.92	5.57	5.27*
	(1.40)	(1.13)	(1.36)
Cardiac index (litre min^{-1} m^{-2})	3.43	3.24	3.06*
	(0.8)	(0.6)	(0.7)
Stroke volume (ml per stroke)	74.3	62.8*	62.4*
	(22.9)	(18.6)	(19.7)
Heart rate (beat min^{-1})	83.1	91.5*	87.5*
	(19.2)	(18.2)	(19.4)
Arterial systolic pressure (mm Hg)	145.4	127.6*	134.9*
	(23.0)	(23.9)	(21.9)
Mean arterial pressure (mm Hg)	97.3	87.1*	92.1*
	(18.3)	(16.2)	(15.7)
Arterial diastolic pressure (mm Hg)	69.8	63.6*	67.4
	(11.5)	(11.4)	(10.9)
PAP, systolic (mm Hg)	21.8	23.6	22.6
	(7.2)	(10.6)	(10.0)
Mean PAP (mm Hg)	11.9	12.5	11.9
	(5.2)	(6.6)	(6.5)
PAP, diastolic (mm Hg)	5.0	6.2	5.7
	(4.3)	(5.7)	(5.8)
CVP (mm Hg)	0.7	1.1	0.7
	(1.1)	(1.7)	(1.2)
PCP (mm Hg)	2.4	3.0	2.2
	(2.7)	(2.9)	(2.3)
Pulmonary artery resistance (dynes s cm^{-5})	133	137	149
	(61)	(67)	(78)
Pulmonary total resistance (dyne s cm^{-5})	168	180	182
	(81)	(85)	(89)
Systemic vascular resistance (dyne s cm^{-5})	1421	1297	1472
	(599)	(451)	(483)
Left ventricular work (kg m min^{-1})	7.49	6.31*	6.32*
	(1.9)	(1.7)	(1.8)

The results were analysed using Student's t test, and considered significant only if P was less than 0.05.

RESULTS

CO and CI had decreased at 3 and 10 min after induction. Significant decreases were also observed in SV. HR increased significantly after administration of etomidate. Systolic, mean and diastolic arterial pressures showed a significant decrease in almost all measurements, while PAP (systolic, diastolic and mean) and the filling pressures (CVP and PCP) showed an increase, notably at 3 min after induction, but the changes were not statistically significant.

No significant changes were observed in the pulmonary or systemic vascular resistances. No atrial or ventricular arrhythmia was observed.

DISCUSSION

Almost all the haemodynamic variables studied were decreased after administration of etomidate, and to a greater extent than described by Bruckner and others (1974) and by Zindler (1975). We observed significant decreases in the stroke volume, which were compensated by an increase in heart rate. The decrease in cardiac output, although statistically significant compared with control, remained within an acceptable range. It is perhaps because of this that the central venous pressure and the pulmonary capillary wedge pressure, indices of ventricular efficiency, did not show important changes. The fact that the mean and diastolic arterial pressures decreased without coincident reduction of the vascular resistances, either pulmonary or systemic, might be invoked as a consequence of the negative inotropism of etomidate. The slight increase in pulmonary arterial pressure and pulmonary vascular resistance recorded 3 min after induction may be because the airway was not yet perfectly established although the simultaneous decreases observed in

Pa_{O_2} might also contribute (Housley et al., 1970; Burrows, 1974).

We may assume that the decreases in cardiac output, stroke volume and arterial pressure elicited by the administration of etomidate during induction of anaesthesia are similar to those described by Etsten and Li (1955), Brown (1961) and Flickinger and others (1961) for barbiturates; by Sonntag and others (1973) and Avello and others (1975) for Althesin; by Dalen and others (1969) and Rao, Shervanink and Prasad (1973) for diazepines and by Johnstone and Barron (1968) and Schenk, Sonntad and Kettler (1974) for propanidid.

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INDUCTION DE L'ANESTHESIE A L'AIDE D'ETOMIDATE: ETUDE HÉMODYNAMIQUE SUR 36 MALADES

RESUME

Les effets hémodynamiques de l'induction de l'anesthésie à l'aide d'étomidate administré par voie intraveineuse ont été évalués sur 36 malades. Les éléments variables étudiés ont été enregistrés dans des conditions de base, de même que 3 et 10 min après l'induction, avant la stimulation chirurgicale. On a constaté une réduction dans le débit cardiaque, le volume systolique et la pression artérielle et une augmentation compensatoire dans la fréquence cardiaque. La pression artérielle pulmonaire et la résistance vasculaire, de même que la pression veineuse centrale ainsi que la pression capillaire pulmonaire en coin sont restées virtuellement inchangées. Bien que l'étomidate ait un effet inotropique négatif, les éléments variables qui étaient déprimés sont, de tout temps, restés dans des limites acceptables.

NARKOSEEINLEITUNG MIT ETOMIDAT: HÄMODYNAMISCHE STUDIE AN 36 PATIENTEN

ZUSAMMENFASSUNG

Die hämodynamischen Wirkungen einer Narkoseeinleitung mit intravenös gegebenem Etomidat wurden bei 36 Patienten beurteilt. Die studierten Variablen wurden unter Ausgangsbedingung, 3 und 10 Minuten nach Verabreichung aufgezeichnet, vor dem Stimulus durch die Operation. Es kam zu Verringerungen von Herzminutenvolumen, Schlagvolumen und arteriellem Druck, mit einem kompensierendem Anstieg der Herztätigkeit. Praktisch unverandert blieben der Lungenarteriendruck, Gefässwiderstand, venöser Druck und Lungenkapillarkeildruck. Obwohl Etomidat einen negativ inotropen Effekt hat, blieben doch alle Werte, die gesenkt wurden, innerhalb akzeptabler Grenzen.

INDUCCION DE ANESTESIA MEDIANTE ETOMIDATE: ESTUDIO HEMODINÁMICO DE 36 PACIENTES

SUMARIO

Se han evaluado los efectos hemodinámicos de la inducción de anestesia en 36 pacientes, mediante etomidate intravenoso. Las variables estudiadas se registraron bajo condiciones basales, y a los 3 y 10 minutos después de la inducción, antes del estímulo quirúrjico. Tuvo lugar una reducción en la producción cardíaca, volumen desplazado y presión arterial, y un incremento compensatorio del ritmo cardíaco. La presión arterial en los pulmones, la resistencia bascular, la presión venosa central y la presión periférica de los capilares pulmonares permanecieron prácticamente sin cambio alguno. Aunque el etomidate posee un efecto inotrópico negativo, aquellas variables que sufrieron reducción permanecieron en todo momento dentro de las tolerancias permitidas.

Br. J. Anaesth. (1980), **52**, 807

PRELIMINARY EXPERIENCE WITH ICI 35 868 AS AN I.V. INDUCTION AGENT: COMPARISON WITH ALTHESIN

K. M. ROGERS, K. M. S. DEWAR, T. D. McCUBBIN AND A. A. SPENCE

SUMMARY

In a small open dose-finding study the i.v. dose of ICI 35 868 required to induce anaesthesia in healthy adults was 2 mg kg^{-1}. Comparison of this dose with Althesin 0.05 ml kg^{-1} for i.v. induction, both injected over 30 s suggests that they have similar effects on heart rate, arterial pressure and breathing. The mean times to loss of eyelash reflex were 57 ± SD 10.1 s (ICI 35 868) and 46 ± SD 3.9 s (Althesin). The new drug was associated with pain and discomfort on injection in seven of 10 patients, but with less involuntary movement than occurred with Althesin.

ICI 35 868 (2 : 6-diisopropylphenol) is a new i.v. anaesthetic drug which has shown promising results in animal studies (Glen, 1980) and in preliminary clinical trials in Belgium (Kay and Rolly, 1977). In 1979 the Committee on Safety of Medicines gave permission for pilot studies of the drug in the U.K. The authors received permission to conduct a double-blind comparison of ICI 35 868 with Althesin as induction agents, on condition that not more than 20 patients received the new drug. The suggested dose of ICI 35 868 1 mg kg^{-1} i.v. (Kay and Rolly, 1977) failed to induce anaesthesia and consequently half of the allocated administrations were deployed in a short dose-finding study from which it was concluded that the appropriate dose was 2 mg kg^{-1}. We report here the results of the open dose-finding study and of the double-blind comparison in 20 patients.

PATIENTS AND METHODS

A total of 30 patients in good general health, aged 17–50 yr and within 10% of the expected body weight gave written permission for the study. None was receiving concurrent drug therapy (including oral contraceptives) and none had a previous history of atopy or allergy. Since the present formulation of ICI 35 868 includes Cremophor EL 16% (w/v) as a solubilizing agent we ensured that no patient had received a previous Cremophor-containing anaesthetic, or indeed any anaesthetic in the past 10 years if the component drugs were unknown. The surgical procedures were all of a simple nature such as the ligation of varicose veins, herniorrhaphy or haemorrhoidectomy.

The anaesthetic procedure was standardized. Premedication was with diazepam 0.15 mg kg^{-1} given orally 60–90 min before induction. The induction agent was given over 30 s into a vein in the back of the hand via a 21-gauge indwelling (butterfly type) needle. At the end of the injection 5 ml of isotonic saline was injected rapidly to clear the dead-space of the needle. If, after 2 min from the start of injection, anaesthesia, judged by abolition of the eyelash reflex, had not been induced (this occurred only with the smaller doses of ICI 35 868) Althesin was injected until the agreed end-point was reached. Two minutes after the start of injection (or immediately following induction of anaesthesia in the patients who required the second injection) a face-mask was applied and anaesthesia was continued with appropriate concentrations of halothane in 70% nitrous oxide in oxygen.

Drug doses

In the initial dose-finding study in 10 patients, ICI 35 868 was given in the following doses: 1 mg kg^{-1} (three patients), 1.5 mg kg^{-1} (four), 2 mg kg^{-1} (two) and 2.5 mg kg^{-1} (one). For the comparative study the dose of ICI 35 868 was 2 mg kg^{-1} and of Althesin 0.05 ml kg^{-1}; at this dose the volume of the Althesin injection would have been half that of the ICI 35 868 preparation and so the Althesin was diluted in an equal volume of isotonic saline to facilitate the double-blind technique. For each patient studied there were two anaesthetist observers and a third anaesthetist who prepared the injections.

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0007-0912/80/080807-04 $01.00

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Measurement and observations in the double-blind study

Induction time: from the start of injection to the abolition of the eyelash reflex.

Symptoms: pain or discomfort on injection, and other clinical observations such as involuntary movements.

E.c.g.: recorded from three conventionally placed chest leads.

Heart rate: counted automatically from the output of an ear-lobe plethysmograph.

Breathing pattern: respiratory frequency and tidal spirogram were obtained using an inductance plethysmograph (Hanning, Smith and Ledingham, 1978). The heart rate, respiratory frequency and spirogram were recorded on a multi-channel Linzeis chart recorder.

Arterial pressure measured with an oscillotonometer was recorded immediately before induction, at 50, 110 and 180 s following the start of injection and at approximately 5-min intervals thereafter.

One and two minutes from the start of injection the response to the application of a sterile towel clip to the medial aspect of the thigh was noted.

Blood sampling. On the day before and on the day after surgery, venous blood was sampled for biochemical and haematological estimations.

Before induction of anaesthesia a 14-gauge cannula was inserted to a vein in the antecubital fossa of the arm opposite to that which was used for drug injection. From some patients who were known, after operation, to have received ICI 35 868, voided urine was collected for a 24-h period in dry sterile bottles. The blood and urine were analysed for the content of the induction drugs or metabolites. The data from this aspect of the study, part of a larger collection, will be presented in a later publication.

Postoperative evaluation. The patient's opinion of both induction and recovery from anaesthesia was sought immediately after wakening and at 24 h after operation. The vein used for the induction injection was examined for signs of tissue damage immediately after injection and after 24 h; each patient was questioned by telephone about the condition of the hand after 3 weeks.

Biochemical and haematological assessment. Biochemical estimations included serum electrolytes, glucose, bilirubin, protein and enzyme indications of liver cell integrity. The haematological survey consisted of haemoglobin, differential white cell count and platelet numbers.

RESULTS

Dose-finding study

On the basis of 10 injections of ICI 35 868 with doses ranging from 1 mg kg^{-1} to 2.5 mg kg^{-1} we concluded that the dose required for induction of anaesthesia in the manner described was approximately 2 mg kg^{-1} (table I).

TABLE I. *Number of patients in whom sleep was induced with different doses of ICI 35 868 i.v. injected over 30 s; nine males and one female**

	Dose (mg kg^{-1})			
	1.0	1.5	2.0	2.5
Awake	2*	3	—	—
Asleep	1	1	2†	1

† Sleep induced in all 10 patients receiving ICI 35 868 in the double-blind study (see text).

Double-blind study

The mean induction times were 46 ± SD 3.9 s for Althesin and 57 ± SD 10.1 s for ICI 35 868. Applying Student's t test this small difference was statistically significant ($P < 0.05$).

The cardiovascular responses to the two drugs were remarkably similar. The average reduction in mean arterial pressure in both groups was approximately 6% at 50 and 110 s after injection compared with the pre-injection baseline (table II). At the same times following injection there was a mean increase in heart rate of 11% following Althesin compared with only 4% following ICI 35 868.

TABLE II. *Effect of induction agents on cardiovascular responses*

	Althesin		ICI 35 868	
	50 s	110 s	50 s	110 s
% Reduction in resting arterial pressure	7.7 ± 5.8	5.6 ± 8.3	4.9 ± 3.2	7.3 ± 4.9
% Increase in resting heart rate	11.8 ± 7.1	10.6 ± 7.7	6.8 ± 7.5	2.6 ± 9.0

Althesin induced a period of apnoea, mean 24 ± SD 4.6 s. Following ICI 35 868 the corresponding values were 38 ± 14.0 s (Student's t test: $P < 0.05$).

Seven of 10 patients receiving ICI 35 868 complained of some form of discomfort in the hand and arm during injection whereas there were no such complaints following Althesin (table III). However, there were no abnormal sequelae in the vein used for injection in any patient.

Involuntary movement occurred in four patients receiving Althesin and one receiving ICI 35 868. The response to application of a towel clip to the leg was similar for the two drugs (table III).

TABLE III. *Sequelae following injection of induction agents*

	Althesin	ICI 35 868
Discomfort on injection		
On questioning	0	7
Spontaneous comment	0	4
Involuntary movement	4	1
Responses to stimulus		
1 min	6	6
2 min	7	8

All of the patients appeared to be satisfied with their experience of the induction of anaesthesia and there were no obvious untoward events such as dreaming or hallucinations.

There were no obvious abnormalities in the haematological data or in the serum electrolyte concentrations before and 24 h after anaesthesia. Neither were there any obvious abnormalities in liver function tests. However, we noted a small increase in the serum bilirubin concentration in seven of the patients who received ICI 35 868. In all but one instance the values remained within the normal range for the hospital laboratory.

DISCUSSION

These preliminary studies indicate that when used in the manner described in this study a suitable induction dose of ICI 35 868 is approximately 2 mg kg^{-1}. However, the method of dose-finding employed by us was crude as a consequence of the limited number of injections which we were permitted to administer. In spite of our uncertainty about the dose, it seemed appropriate to compare our initial experience of the new agent with Althesin as an example of a better known i.v. anaesthetic, the pharmacological profile and formulation of which was not dissimilar to that of the new compound.

The results suggest that, as with Althesin, ICI 35 868 provides a reliable induction of anaesthesia with no unpleasant after-effects. Although no patient found the experience unpleasant in retrospect, the complaints of pain in the hand and arm during injection of ICI 35 868 must be regarded as an important disadvantage of the compound. It may be that changes in the formulation can lead to a lessening of this problem. The cardiovascular stability associated with ICI 35 868 was impressive. The respiratory depression produced by the new compound was slightly more marked than that with Althesin, but we would not regard this as a serious disadvantage in clinical practice.

The pharmacokinetic profile of ICI 35 868 in animals (Adams, Glen and Hoyle, 1980) indicates a compound that might be expected to provide rapid recovery from anaesthesia and to be particularly suitable for administration to outpatients. Similarly, a compound with these characteristics would be worthy of evaluation as a continuous i.v. anaesthetic although it is not possible to predict from the present studies that it would be a satisfactory anaesthetic if used as the sole agent.

ACKNOWLEDGEMENTS

We wish to acknowledge the help of Mr Robert Watson, the technicians of the University Department of Anaesthesia, the resident medical staff of Wards G6 and 7, Western Infirmary and ICI Pharmaceuticals Ltd, for supplies of ICI 35 868.

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EXPERIENCE PRELIMINAIRE AVEC ICI 35 868 UTILISE COMME AGENT D'INDUCTION PAR VOIE INTRAVEINEUSE: COMPARAISON AVEC L'ALTHESINE

RESUME

Au cours d'une petite étude libre pour trouver les doses appropriées, la dose d'ICI 35 868 requise pour provoquer l'anesthésie sur des adultes en bonne santé a été de 2 mg kg^{-1}. La comparaison de cette dose avec l'althésine administrée à raison de 0,05 ml kg^{-1} pour l'induction par voie intraveineuse, toutes deux injectées en moins de 30 s, laisse penser qu'elles ont des effets similaires sur la fréquence cardiaque, la pression artérielle et la respiration. Les temps moyens pour arriver à la perte du réflexe de cillement ont été de 57 s ± erreur type 10,1 s (pour ICI 35 868) et de 46 s ± erreur type de 3,9 s (pour l'althésine). Le nouvel agent a été associé à des douleurs et des malaises au moment de l'injection sur 7 patients sur 10, mais à moins de mouvements involontaires tels que ceux qui se sont produits avec l'althésine.

ERSTE ERFAHRINGEN MIT ICI 35 868 ALS INTRAVENÖSEM NARKOSEEINLEITUNGSMITTEL: VERGLEICH MIT ALTHESIN

ZUSAMMENFASSUNG

In einer kleinen offenen Studie zur Dosisfeststellung von intravenös gegebenem ICI 35 868 zur Einleitung von Narkose war die erforderliche Dosis bei gesunden Erwachsenen 2 mg kg^{-1}. Ein Vergleich dieser Dosis mit Althesin 0,05 ml kg^{-1}, beide uber 30 sek injiziert, zeigt, dass die Drogen ähnliche Wirkungen auf die Herztätigkeit, den arteriellen Druck und die Atemtätigkeit haben. Die mittlere Zeit für den Verlust des Lidreflexes war 57±SD 10,1 sek (ICI 35 868) und 46±SD 3,9 sek (Althesin). Die neue Droge bewirkte Schmerzen und Unbehagen bei der Injektion bei sieben von 10 Patienten, aber bei weniger unwillkurlichen Bewegungen als bei Althesin.

EXPERIENCIA PRELIMINAR CON ICI 35 868 A GUISA DE AGENTE INTRAVENOSO DE INDUCCION: COMPARACION CON LA ALTESINA

SUMARIO

Durante un pequeño estudio para averiguar la dosis necesaria para inducir anestesia en adultos sanos, mediante ICI 35 868, se concluyó que ésta era de 2 mg kg^{-1}. La comparación de estas dosis con 0.05 ml kg^{-1} de altesina para producir inducción intravenosa, ambas dosis inyectadas a lo largo de 30 segundos, sugirió que estas cantidades ejercían efectos similares sobre el ritmo cardiaco, la presión arterial y la respiración. El promedio de tiempo para perder el reflejo del párpado fue de 57±desviación típica de 10,1 (para el ICI 35 868) y de 46±desviación típica de 3,9 (para la altesina). La inyección de la neuva droga vino asociada con dolor y molestias en 7 de los 10 pacientes, pero con un menor movimiento involuntario que el acaecido con la altesina.

Br. J. Anaesth. (1980), **52**, 811

SEDATION FOR UPPER GASTRO-INTESTINAL ENDOSCOPY

A comparison of oral temazepam and i.v. diazepam

J. G. Douglas, W. S. Nimmo, R. Wanless, D. R. Jarvie, R. C. Heading and N. D. C. Finlayson

SUMMARY

Temazepam 20 mg orally was compared with titrated doses of i.v. diazepam as sedation for elective upper gastro-intestinal endoscopy. The mean time from taking oral temazepam to endoscopy was 66 min, and from i.v. diazepam to endoscopy was 10 min. The endoscopists found that the sedation achieved was the same in both groups and allowed adequate examination of the upper alimentary tract. The oral presentation, avoiding the pain of injection and the possible shorter duration of action, made oral temazepam preferable to i.v. diazepam.

Although upper gastro-intestinal endoscopy can be performed without sedation (Beavis, Brooy and Misiewicz, 1979), premedication increases patient acceptability and facilitates the examination (Galizia, Metreweli and Prout, 1975; Editorial, 1976; Hoare and Hawkins, 1976; Le Brun, 1976). Ideally, the premedication should reduce anxiety without causing respiratory or cardiovascular depression and should have a short duration of action. I.v. diazepam is widely used, but its effect is unpredictable (Dundee and Haslett, 1970; Hoare and Hawkins, 1976; Whorwell, Smith and Foster, 1976). It may produce pain on injection with subsequent thrombophlebitis (Langdon, Harlan and Bailey, 1973) and has a long duration of action (Klotz et al., 1975; Mandelli, Tognoni and Garattini, 1978). Temazepam (3-hydroxydiazepam), a metabolite of diazepam, is rapidly absorbed when taken orally and peak plasma concentrations are reached within 1 h of administration. It is an effective hypnotic and has a shorter duration of action (Nicholson and Stone, 1976; Pines et al., 1976; Fucella et al., 1977).

We report a comparison of a standard dosage of oral temazepam with titrated doses of i.v. diazepam as premedication for elective endoscopy.

PATIENTS AND METHODS

Eighty-one consecutive patients without evidence of oesophageal stricture or pyloric stenosis and undergoing elective upper gastro-intestinal endoscopy were randomly allocated to two groups (table I). One group received temazepam 20 mg orally approximately 60 min before endoscopy and an i.v. injection of placebo (saline) immediately before the procedure. Patients in the other group received two placebo capsules 60 min before endoscopy and an i.v. injection of diazepam immediately before the endoscope was passed. The diazepam was given over 2 min to an end-point of slurred speech, disorientation or ptosis, or to a maximum dose of 20 mg. Neither the patient nor the endoscopist knew which premedication was to be given. All patients received atropine 0.6 mg i.v. to reduce pharyngeal secretions; the pharynx was anaesthetized with 10% lignocaine spray. Endoscopy was performed with the patient supine using either an Olympus GIFK or an Olympus GIFP2 panendoscope.

The endoscopist graded patient co-operation in swallowing the instrument, relaxation during the examination and gastric peristalsis. Coughing and the need to aspirate pharyngeal secretion were also recorded. The anaesthetist monitored the patient's heart rate, arterial pressure and respiratory rate before premedication, immediately after the i.v. injection and again at 5 min, 20 min and 2 h. Before premedication and again 2 h after endoscopy, patients were asked to perform a pegboard test and to delete every letter "e" from a paragraph of typed print in 30 s. In addition each patient was shown a picture of an object such as a cup or a car immediately before endoscopy and 2 h later was questioned about the procedure and asked to name the object. The patient was asked if he or she would be willing to undergo repeat endoscopy. Statistical analyses were performed using χ^2 test, unless otherwise specified.

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0007-0912/80/080811-05 $01.00

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TABLE I. *Patients and premedications.* * *All patients received atropine* 0.6 *mg*

Patients							Premedication				
Group	M	F	Mean age (yr)	Mean wt. (kg)	In-patient	Out-patient	Drug*	Mean dose ± SEM (mg)	Time from capsule to endoscopy (min) (mean ± SEM)	Time from i.v. injection to endoscopy (min) (mean ± SEM)	Duration of endoscopy (min) (mean ± SEM)
A ($n = 41$)	27	14	47	67	8	33	Temazepam	20	66 ± 4	9.5 ± 1.1	19.7 ± 1.1
B ($n = 40$)	28	12	54	66	11	29	Diazepam	12.1 ± 0.8	57 ± 4	9.9 ± 1.1	24.4 ± 1.3

Blood was taken at intervals and plasma concentrations of temazepam were measured by high-performance liquid chromatography (HPLC).

Analytical method

Temazepam, oxazepam, diazepam and desmethyldiazepam were measured simultaneously by a modification of the method of Kabra, Stevens and Marton (1978). The drugs were extracted into dichloromethane from alkaline plasma, the extracts evaporated and the residues dissolved in HPLC solvent before injection into a column of ODS-Hypersil 5 μm microspheres (Shandon Southern Products Ltd, Cheshire). HPLC solvent was a mixture of methanol and sodium acetate buffer 0.01 mol litre^{-1}; pH 4.6; 60 : 40 v v. Carbamazepine was used as internal standard. Detection limit was 5 μg litre^{-1}.

RESULTS

The groups were similar with regard to age, sex, weight, source of referral and duration of endoscopy. There was no significant difference in patient co-operation and relaxation with either endoscope.

Endoscopist's assessment

There were no statistically significant differences in patient co-operation, relaxation or gastric peristalsis during the procedure (table II). Three patients (two male, one female) who were given i.v. diazepam (average dose 10.8 mg) were initially unco-operative and required further i.v. diazepam. One

TABLE II. *Endoscopist's assessment of the premedication.* * *One not recorded because endoscopy abandoned. Comp = complete; Adeq = adequate; Pres = present; Vig = vigorous; Occ = occasional; Disr = disruptive; suc = Suction required*

	Co-operation				Peristalsis			Relaxation			
Premedication	Comp	Adeq	Poor	None	None	Pres	Vig	Comp	Adeq	Poor	None
Oral temazepam ($n = 41$)	16	21	4	0	4	33	4	13	24	4	0
I.v. diazepam ($n = 40$)	16	12	9	3	12	21	6*	14	20	4	1*

	Cough				Secretion		
Premedication	None	Occ (<3)	Freq (>3)	Disr	None	Occ	Suc
Oral temazepam ($n = 41$)	35	5	1	0	36	5	0
I.v. diazepam ($n = 40$)	23	9	6	1*	33	5	1*

patient remained unco-operative and endoscopy was abandoned. No patient given oral temazepam needed further sedation.

In both groups, coughing and excess pharyngeal secretion were rare and in only one patient given diazepam was this disruptive. In only three cases (two after temazepam and one after placebo capsules) was the capsule seen during the procedure. One patient had achalasia of the cardia, another had atrophic gastritis and the third had a normal endoscopy. The mean time from taking the capsule to the start of endoscopy in these three patients was 67.7 min, which was similar to the 61.7 min for all 81 patients studied.

Anaesthetist's observations

Predictably, the heart rate increased immediately after i.v. atropine and decreased after endoscopy in both groups. There were no important changes of systolic arterial pressure or respiratory rate in either group, although both increased slightly during endoscopy.

Patients' assessment

Pain at the site of i.v. injection or further up the arm occurred in 15 patients (38%) given i.v. diazepam (table III). This was significantly more frequent ($P<0.01$) than in those given temazepam, of whom only two (5%) complained of any pain during placebo injection.

Patients who received temazepam had significantly greater recall of the endoscopy than had the patients who received diazepam ($P<0.01$). Similar results were obtained for recall of the picture shown to all patients immediately before the endoscopy. However, almost all patients in both groups were willing to undergo repeat endoscopy.

Performance of the pegboard test took slightly longer after endoscopy than before the examination in the patients given diazepam, but there was no difference in those given temazepam. In both groups, however, there was a reduction in the number of letters deleted in 30 s, 2 h after endoscopy.

Plasma concentrations of temazepam

In only one patient in the temazepam group was temazepam not detectable in plasma at the time of endoscopy. However, the capsule had been given only 15 min previously. Mean ± SEM plasma temazepam concentrations at the time of endoscopy and 2 h after endoscopy were 319.3 ± 18.5 µg litre^{-1} and 171.1 ± 10.4 µg litre^{-1} respectively. Plasma concentrations of oxazepam at these times were 8.1 ± 1.1 µg litre^{-1} and 9.2 ± 1.2 µg litre^{-1}.

DISCUSSION

We compared a standard oral dose of temazepam with i.v. diazepam in a dose carefully titrated against response and both premedications were satisfactory.

TABLE III. *Patients' assessment of the procedure. (SEM in parentheses.) * Given saline 5 ml as placebo injection. † No significant difference from before premed. **Significantly different from before premed. Recog =picture recognized if shown.* (P < 0.01, *paired* t *test*)

	Pain on i.v. injection		Ability to recall procedure			Recall of picture		
Premedication	No	Yes	None	Some	Total	None	Recog	Total
Oral temazepam (*n* = 41)	39	2*	0	3	38	2	1	38
I.v. diazepam (*n* = 40)	25	15	7	15	18	23	9	8

	Would have again?		Mean time to do pegboard test (s)		Mean no. of e's deleted in 30 s	
Premedication	Yes	No	Before premed	2 h after endoscopy	Before premed	2 h after endoscopy
Oral temazepam (*n* = 41)	36	5	75.5 (±3.7)	74.9 (±3.9)†	21.5 (±1.2)	18.8 (±1.0)**
I.v. diazepam (*n* = 40)	36	4	84.2 (±4.9)	95.2 (±5.9)**	17.8 (±1.4)	14.3 (±1.0)**

Although temazepam has been used extensively as a hypnotic, there are no reports of its use as a premedication for endoscopy.

There were few differences between the two premedications. Although it appeared that patient co-operation was better after temazepam, this was not substantiated statistically. However, in three patients given diazepam, endoscopy was impossible initially because of lack of co-operation. Two of these patients became more co-operative after a further dose of diazepam, but one patient remained unco-operative and endoscopy had to be abandoned.

Diazepam produced significantly greater amnesia than did temazepam. Although there is an association between amnesia and patient acceptability (Nimmo et al., 1978) almost all of the patients were willing to undergo repeat endoscopy after either temazepam or diazepam.

The majority of those studied were outpatients and all were fully conscious and orientated 2 h after endoscopy. All were able to go home accompanied at that time. The effects of temazepam may have been of shorter duration than those of diazepam, however, since the time to transfer pegs in a pegboard was the same 2 h after endoscopy as before sedation. The patients who received diazepam took longer to complete the test 2 h after endoscopy.

Oral premedication avoided the complication of pain experienced by 38% of the patients receiving diazepam i.v. Although all the patients received atropine i.v. this might be replaced by hyoscine orally, or perhaps omitted.

The oral route is more convenient and safer than the i.v. route. Overdosage is much less likely. Oral temazepam, in a fixed dosage, is as effective as titrated doses of i.v. diazepam and does not harm veins. Thus, in patients without evidence of pyloric stenosis or oesophageal obstruction, which would delay absorption, it is our preferred premedication for upper gastro-intestinal endoscopy. It deserves further study in other procedures in which i.v. diazepam is used as sedation.

ACKNOWLEDGEMENT

We are grateful to Wyeth Laboratories for supplies of temazepam and placebo capsules.

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SEDATION EN VUE D'UNE ENDOSCOPIE GASTROINTESTINALE SUPERIEURE

Une comparaison entre le temazepam oral et le diazepam i.v.

RESUME

On a comparé 20 mg de temazepam oral avec des doses titrées de diazepam i.v. comme moyen de sédation dans l'endoscopie gastro-intestinale supérieure élective. La durée moyenne entre l'administration orale de témazepam et l'endoscopie était de 66 min et entre l'administration i.v. de diazepam et l'endoscopie de 10 min. Les responsables de l'endoscopie se sont rendu compte que la sédation obtenue était la même dans les deux groupes et permettait l'examen approprié du tract alimentaire supérieur. Le produit oral qui évite la douleur de la piqûre et la moindre durée d'action possible font du témazepam oral une substance préférable au diazepam i.v.

BERUHIGUNGSMASSNAHMEN BEI OBERER GASTROINTESTINALER ENDOSKOPIE

ZUSAMMENFASSUNG

Temazepam, per os in einer Dosis von 20 mg verabreicht, wurde mit titrierten Dosen von intravenösem Diazepam als Beruhigungsmittel bei ausgewählten oberen gastrointestinalen Endoskopien verglichen. Die durchschnittliche Zeit zwischen Verabreichung per os von Temazepam und Endoskopie betrug 66 Minuten; zwischen intravenöser Injektion von Diazepam und Endoskopie betrug die Zeit 10 Minuten. Es wurde dabei festgestellt, dass das dadurch erreichte Beruhigungsgrad bei beiden Gruppen gleich gross war und eine hinreichende Untersuchung der oberen Verdauungswege gestattete. Infolge der peroralen Verabreichung von Temazepam, unter Vermeidung schmerzhafter Injektionen und einer möglicherweise kürzeren Wirkungsdauer, ist dieser dem intravenosen Diazepam vorzuziehen.

SEDACION PARA ENDOSCOPIA GASTRO-INTESTINAL SUPERIOR

Una comparación entre el temazepam oral y el diazepam i.v.

SUMARIO

Se hizo una comparación entre 20 mg de temazepam oral y dosis tituladas de diazepam i.v. como sedación para endoscopia gastro-intestinal superior electiva. El tiempo promedio entre la administración oral de temazepam y la endoscopia era de 66 min y entre el diazepam i.v. y la endoscopia 10 min. Los endoscopistas se dieron cuenta que la sedación obtenida era igual en ambos grupos y permitía un examen adecuado del sistema alimenticio superior. La presentación oral que elimina el dolor de la inyección y la posible duración menor de la acción hacen que el temazepam oral resulte preferible para con el diazepam i.v.

Br. J. Anaesth. (1980), **52**, 817

LOCAL REACTIONS AFTER I.V. INJECTIONS OF DIAZEPAM, FLUNITRAZEPAM AND ISOTONIC SALINE

H. Mikkelsen, T. M. Hoel, H. Bryne and C. D. Krohn

SUMMARY

Local reactions after i.v. injection of diazepam, flunitrazepam and isotonic saline were studied in patients who received extradural analgesia or general anaesthesia. The frequency of thrombophlebitis on the 1st, 3rd and 5th days after the injection of diazepam was 2.1%, 17.0% and 14.9% respectively, after flunitrazepam 10.0%, 10.0% and 14.0%, and after saline 0%, 6.7% and 4.4%. The differences between the groups were not statistically significant ($P > 0.05$). One month after the injection 15.6% in the diazepam group, 8.5% in the flunitrazepam group and 9.3% in the saline group had pain or tenderness in the arm used for the injection.

Local reactions after the i.v. injection of benzodiazepines are well known. However, the frequency of reactions differs from one study to another. Hegarty and Dundee (1977) showed that diazepam caused a greater frequency of reactions than flunitrazepam or lorazepam.

We have compared the frequency of local reactions after i.v. diazepam, flunitrazepam and isotonic saline. Isotonic saline was included to ascertain the role of mechanical irritation.

METHODS

One hundred and forty-two patients aged 22–85 yr receiving extradural analgesia or general anaesthesia were studied. The mean age of patients in the diazepam group was 44.9 yr, in the flunitrazepam group 46.8 yr and in the saline group 50.5 yr. Verbal consent was given by each patient. An 18-gauge plastic cannula was inserted to the cephalic vein at the wrist, and either diazepam 5 mg (Valium, Roche), flunitrazepam 1 mg (Rohypnol, Roche) or isotonic saline 1 ml was given in 1 min. Each injection comprised 1 ml of fluid. After about 15 min the dose was repeated, and the cannula withdrawn. No other drug or fluid was injected to the same arm during the hospital stay. If further sedation was required during the operation, this was given through an indwelling cannula in the other arm.

On the 1st, 3rd and 5th days after operation the vein was inspected and palpated at the injection site and proximally, and the presence or absence of tenderness, erythema, oedema or thickening of the vein noted. The degree of tenderness was graded from 1 to 3, 1 denoting slight, 2 moderate and 3 severe tenderness. Thrombophlebitis was defined as the presence of two or more of these signs. Neither the examiner nor the patient knew the identity of the injected drug. About 1 month after the operation the patients were sent a questionnaire enquiring about pain or tenderness, redness, swelling and any limitation of daily activity because of these symptoms.

The Wilcoxon two-sample rank sum test with corrections for tied observations was used for comparison with respect to degree of tenderness; a two-sided test was used to compare diazepam with flunitrazepam, and a one-sided test for comparison with placebo. The Fisher–Irwin test was used for comparison with respect to the frequency of erythema, oedema, swelling and thrombophlebitis; a two-sided test was used to compare diazepam with flunitrazepam and a one-sided test for comparison against placebo.

RESULTS

The results are shown in tables I and II. On the 5th day after operation, local tenderness was present in 10 of the 47 patients receiving diazepam, in nine of the 50 patients receiving flunitrazepam and in five of the 45 receiving saline. Seven patients in the diazepam group, seven in the flunitrazepam group and two in the saline group had localized thrombophlebitis on the 5th day after operation. None of the differences between the groups was statistically significant ($P > 0.05$).

In response to the questionnaire, seven patients in the diazepam group, four in the flunitrazepam group

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0007-0912/80/080817-03 $01.00

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TABLE I. *Local reactions at the injection site and proximally along the vein.* *1,2,3 = *degree of tenderness*

		I.v. agent					
		Diazepam		Flunitrazepam		Saline	
Sign	Day	No.	%	No.	%	No.	%
Tenderness	1						
1*		1	2.1	5	10.0	2	4.4
2*		1	2.1	—	—	—	—
3*		—	—	—	—	—	—
Total		2	4.3	5	10.0	2	4.4
Tenderness	3						
1*		8	17.0	2	4.0	3	6.7
2*		1	2.1	2	4.0	1	2.2
3*		—	—	—	—	—	—
Total		9	19.1	4	8.0	4	8.9
Tenderness	5						
1*		7	14.9	5	10.0	5	11.1
2*		2	4.3	4	8.0	—	—
3*		1	2.1	—	—	—	—
Total		10	21.3	9	18.0	5	11.1
Erythema	1	—	—	—	—	—	—
	3	2	4.3	1	2.0	3	6.7
	5	2	4.3	3	6.0	—	—
Oedema	1	—	—	4	8.0	—	—
	3	2	4.3	4	8.0	—	—
	5	1	2.1	2	4.0	1	2.2
Thickening of vein	1	2	4.3	7	14.0	1	2.2
	3	8	17.0	6	12.0	3	6.7
	5	7	14.9	9	18.0	4	8.9
Thrombophlebitis	1	1	2.1	5	10.0	—	—
	3	8	17.0	5	10.0	3	6.7
	5	7	14.9	7	14.0	2	4.4
Total number of patients		47		50		45	

TABLE II. *Answers to the questionnaire*

	I.v. agent					
	Diazepam		Flunitrazepam		Saline	
Symptom	No.	%	No.	%	No.	%
Pain or tenderness	7	15.6	4	8.5	4	9.3
Redness	2	4.4	2	4.3	1	2.3
Swelling	2	4.4	1	2.1	—	—
Handicapped	3	6.7	—	—	3	7.0
Number of answers	45		47		43	

and four in the saline group reported pain or tenderness. Two patients in the diazepam group, three in the flunitrazepam group and two in the saline group did not return the questionnaire.

DISCUSSION

The frequency of local venous reactions after i.v. benzodiazepines varies considerably from one study to another. These differences are most likely to be a result of different injection rates, sizes of veins used, solvents, observation times and the criteria for defining reactions. Age may also exert an influence (Hegarty and Dundee, 1977). Langdon, Harlan and Bailey (1973) noted a frequency of only 3.5% after i.v. diazepam. Hegarty and Dundee (1977) detected venous sequelae after diazepam in 23% of patients after 2–3 days and in 39% after 7–10 days. This time-related increase in frequency during the first days after injection was noted also by Siebke, Ellertsen and Lind (1976) and was confirmed in the present study.

In the first two studies above, the frequency of reactions was greater when small veins were used for the injection. We tried to use one distinct vein present in most patients, namely the cephalic vein at the wrist. In most of our patients it was relatively large.

Hegarty and Dundee (1977) found only 5% sequelae after flunitrazepam, compared with 39% after diazepam. We did not detect this difference between diazepam and flunitrazepam. A clue to this could be the frequency of reactions demonstrated in the saline group. This may be attributed to mechanical irritation by the relatively large cannula at venepuncture and to endothelial damage caused by the cannula while lying in the vein. However, the frequency of reactions after diazepam in our study is lower than that found by Hegarty and Dundee, and thus it is unlikely that this is the sole reason for the different findings.

The solvent used in the preparations may play a role in producing the reactions. In our study, both benzodiazepines had propylene glycol as the solvent, 414 mg ml^{-1} in both solutions. The flunitrazepam preparation used by Hegarty and Dundee (1977) was made by the same manufacturer as the preparation used in this study, so we assume that the solvent is the same and in the same amount. We understand the preparation of diazepam used by Hegarty and Dundee was the usual formulation in propylene glycol, so that differences between the formulations used are unlikely to acount for the difference in results.

The questionnaire did not enquire about the presence of a painless, thin cord-like vein which often results from thrombophlebitis; it would be difficult for a patient without special knowledge of anatomy to detect this sign. However, the omission of this feature could cause an under-estimation of the late sequelae of diazepam administration.

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REACTIONS LOCALES APRES L'NJECTION INTRAVEINEUSE DE DIAZEPAM, DE FLUNITRAZEPAM ET DE SOLUTION PHYSIOLOGIQUE

RESUME

On a étudié les réactions locales après l'injection intraveineuse de diazépam, de flunitrazépam et de solution physiologique sur des malades auxquels on avait administré une analgésie extradurale ou une anesthésie générale. Le fréquence de thrombophlébite, les 1er, 3ème et 5ème jours après l'injection de diazépam ont été respectivement de 2,1%, 17% et 14,9%. Après le flunitrazépam, ces chiffres ont été de 10%, 10% et 14% alors qu'après la solution physiologique ils ont été de 0%, 6,7% et 4,4%. Les différences entre les groupes n'ont eu aucune signification statistique ($P < 0,05$). Un mois après l'injection, 15,6% du Groupe diazépam, 8,5% du Groupe flunitrazépam et 9,3% du Groupe solution physiologique, souffraient de douleurs ou de sensibilité au toucher dans le bras utilisé pour l'injection.

LOKALREAKTIONEN NACH INTRAVENÖSEN INJEKTIONEN VON DIAZEPAM, FLUNITRAZEPAM UND ISOTONISCHEN KOCHSALZLÖSUNGEN

ZUSAMMENFASSUNG

Solche Reaktionen wurden bei Patienten studiert, die einer extraduralen Analgesie oder einer Algemeinen Narkose unterzogen wurden. Die Häufigkeit von Thrombophlebitis and den Tagen 1, 3 und 5 nach der Diazepam-Injektion betrug jeweils 2,1%, 17,0% und 14,9%: nach Flunitrazepam jeweils 10,0%, 10,0% und 14,0%, und nach Kochsalz 0%, 6,7% und 4,4%. Die Unterschiede zwischen den Gruppen waren statistisch gesehen nicht signifikant ($P > 0,05$). Einen Monat nach der Injektion klagten 15,6% der Diazepam-Gruppe, 8,5% der Flunitrazepam-Gruppe und 9,3% der Kochsalz-Gruppe uber Schmerzen oder Empfindlichkeit im Injektionsarm.

REACCIONES LOCALES DESPUES DE INYECCION I.V. DE DIAZEPAM, FLUNITRAZEPAM Y SOLUCION SALINA ISOTONICA

SUMARIO

Se estudió las reacciones locales después de la inyección i.v. de diazepam, flunitrazepam y solución salina isotónica en pacientes a quienes se administró analgesia extradural o anestesia general. La frecuencia de la tromboflebitis el 1ro, el 3ro y el 5o día después de la inyección de diazepam se estableció en 2,1%, 17,0% y 14,9% respectivamente, después del flunitrazepam en 10,0%, 10,0% y 14,0%, y después de la solución salina en 0%, 6,7% y 4,4%. Las diferencias entre los grupos no eran significativas desde el punto de vista estadístico ($P < 0,05$). Un mes después de la inyección, el 15,6% del grupo diazepam, el 8,5% del grupo flunitrazepam y el 9,3% del grupo solución salina tenían dolor o sentían dolor a la presión en el brazo donde se había practicado la inyección.

Br. J. Anaesth. (1980), **52**, 821

EXPERIENCES WITH LUMBAR EXTRADURAL ANALGESIA FOR CAESAREAN SECTION

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SUMMARY

The results of 324 Caesarean sections conducted under lumbar extradural block are discussed. In addition to pre-loading with fluid i.v. and the avoidance of aorto–caval compression, more recent modifications have been to administer bupivacaine in incremental doses, to be less concerned with the size of the total dose, and to provide the mother with supplementary oxygen until delivery. As a result of these modifications, the frequency of maternal discomfort and hypotension has been reduced, and the need for supplementary analgesia or a vasopressor has become a rarity. Administration of diazepam after delivery is still occasionally advisable. The technique has many advantages for both mother and infant and with a good obstetric service, few disadvantages. Prolongation of the interval between incision of the myometrium and delivery appears to be less detrimental to the infant than is the case when general anaesthesia is used.

Growing interest in the provision of lumbar extradural analgesia for labour and vaginal delivery has led to the use of the technique as an alternative to general anaesthesia for Caesarean section. An account is presented of experience of the technique in one busy maternity hospital.

SUBJECTS AND METHODS

Occasional patients were operated on for Caesarean section under lumbar extradural block from 1968, but it was not until the mid 1970's that sections were conducted in this manner on a regular basis. By that time, experience in other areas of obstetric anaesthesia had shown the necessity of ensuring that patients were not exposed to aorto–caval compression and that adequate circulating volume was maintained. From the outset of the series discussed, patients undergoing elective section were pre-loaded with Hartmann's solution 1–2 litre while those awaiting emergency section were given additional i.v. fluid as required. Patients in both groups were tilted laterally, the direction of tilt determined by the mother's arterial pressure (James et al., 1977).

Previously, all or the major portion of the dose of bupivacaine 0.5% without adrenaline was administered as a single injection via the extradural cannula with the mother lying in the lateral position, first on one side then, 5–10 min later, on the other. The total dose was usually only sufficient to provide sensory loss to the level of T6–T7. Most mothers breathed room air throughout the period of the operation and ergometrine with or without oxytocin was administered after delivery. Dissatisfaction with this method of management led to the adoption of a new technique which has been used since the end of 1977.

For elective section, bupivacaine 0.5% without adrenaline is injected in incremental doses after adequate fluid administration. The first dose (usually 10 ml) is given whilst the patient reclines against a head-rest. The second dose (usually 5 or 10 ml) is given not less than 10 min later, with the patient lying in the lateral position. Not less than 10 min after the second dose the patient is turned on to her other side and, if necessary, additional doses are administered. Only when loss of skin sensation to T6 has been achieved is the patient taken into the operating theatre. Far less regard than previously is paid to attempts to ensure a small total dose. Additional features of the modified technique have been that the mother is provided with supplementary oxygen until the infant has been delivered, and that ergometrine is not given unless considered by the obstetrician to be essential. If oxytocin therapy is required, it is administered i.v. either as a dilute bolus (5–10 units) or by infusion.

Rarely, an extradural block already in progress for labour was considered to have spread far enough cephalad to allow the operation to be started without a supplement, but more frequently an incremental dose of bupivacaine—usually 10 ml, sometimes 20 ml—was required. Most of the patients who

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0007-0912/80/080821-05 $01.00

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underwent emergency section under extradural block had an extradural cannula in place before the decision to operate was made. In a few instances, the condition of both mother and fetus was such that there was sufficient time to initiate a block specifically for emergency section.

RESULTS

There have been 142 elective Caesarean sections and 182 emergency sections from 1973 to the autumn of 1979. For patients undergoing elective section, the total dose of bupivacaine has ranged from 15 ml to 55 ml, administered as one to six injections. As stated above, the technique evolved gradually, so the fact that the mean dose of bupivacaine in the entire series is 26.3 ml is of little significance. During the period 1978–79, 70 cases of elective section were conducted using the present technique, and the mean dose was 27.2 ml.

The time from the first dose of bupivacaine to delivery by elective section in minutes, ranged from 25 to 183, mean 74.3, and that from the final dose to delivery ranged from 3 to 112, mean 36.8.

There was a failure to establish satisfactory extradural analgesia in three patients, who are not included in this report.

Three patients undergoing elective section received a general anaesthetic after delivery. One (who had received bupivacaine 30 ml in increments of 15, 10 and 5 ml) because she complained of discomfort in her legs. The second received 30 ml in two doses (20 ml and 10 ml), and reported considerable pain at the site of surgery. The third patient complained of pain on incision of the peritoneum and had received 20 ml (10 ml and 10 ml). Neither of the last two patients had received the first dose of bupivacaine whilst semi-reclining. Seven patients required additional analgesia after delivery because of suprapubic pain. The details of the dose (ml) of bupivacaine, are as follows:

Patient	Increments	Total
1	15 5	20
2	15 5	20
3	20	20
4	10 6	16
5	10 5 5 5 5 5	35
6	10 10 10 5 5	40
7	10 6 4 5	25

Each of these patients was given pethidine 50 mg i.v. and 50% nitrous oxide in oxygen was also administered to patients 1 and 2. Only patient 7 was anaesthetized during the period 1978–79; the remainder did not have a dose of bupivacaine injected whilst in the semi-reclining position. The requirements for supplementation are summarized in table I.

TABLE I. *Number of occasions during elective Caesarean section when pain during the operation required the administration of general anaesthesia or pethidine or nitrous oxide (analgesia). The operations are divided into those conducted under the present "incremental technique" of extradural block and those managed under the earlier technique*

	n	General anaesthesia	Analgesia
Earlier technique	72	2	6
Present technique	70	0	1

Three patients undergoing emergency section required general anaesthesia after delivery. In one of these the level of sensory block reached only to T10, and in retrospect it would clearly have been wiser either to delay operation until another dose had been given, or to have administered general anaesthesia from the start. Four patients required supplementary analgesia—pethidine in three patients and nitrous oxide in the fourth.

In one patient general anaesthesia had been the first choice, but endotracheal intubation proved impossible, so the mother was allowed to waken and an extended block was given via a previously inserted extradural cannula.

Eight patients undergoing elective section had been given a vasopressor (ephedrine). Each of the episodes of hypotension occurred before the introduction of the present technique, and most followed an initial injection of bupivacaine 20 ml. Two patients in the series of elective sections developed marked bradycardia and were given atropine 0.6 mg i.v. with satisfactory results.

One patient in the series of emergency sections was successfully treated with ephedrine and atropine for severe hypotension which occurred immediately after delivery. Blood loss at the time was estimated to be 600 ml, and she had received almost 2 litre of Hartmann's solution. One other patient developed severe bradycardia which responded to atropine.

One of the few complications encountered since the development of this technique has been that the mother tends to become restless after the baby has been born. Minor discomforts then achieve prominence—heaviness of the legs, backache, stiffness in the elbows and shoulders. The presence of the husband sitting at the head of the table (a practice which has been encouraged unless there are obvious clinical or personality reasons for not doing so) has helped to alleviate this, as also has the anaesthetist who sustains the mother's morale by appropriate conversation. A further aid has been the provision of music from a cassette recorder.

The maternal satisfaction with this management has been impressive. The mother sees her baby when it is delivered; often she can hold it (even to the breast) within minutes of delivery, and can continue to be closely aware of it throughout the remainder of the operation and in the period immediately after operation.

Maternal nausea and retching were very uncommon features during operation after the abandonment of the use of ergometrine except under the most extreme circumstance of uterine hypotonia. Perphenazine was administered to many of the patients, but this has been a precaution rather than an essential prophylactic.

The extradural cannula was used for analgesia after operation in some patients, but a shortage of nursing staff has been a limiting factor. Furthermore, it has not always been appreciated that when the patient is no longer pregnant the volume of bupivacaine solution required to provide a sufficient block is considerably more than the usual top-up dose. A dose of less than 15–20 ml of 0.25% bupivacaine would be unlikely to eliminate abdominal pain after surgery. Whether or not an injection has been given after operation, mobility of the mother after operation has, in general, been more prompt and more energetic than that seen after sections conducted under general anaesthesia.

Detailed reference to the condition of the infants is confined to those delivered by elective section. Only the Apgar minus colour scores at 1 and 5 min ($(A-C)_1$ and $(A-C)_5$) are considered since the available acid–base data are insufficient to report.

Eighteen infants had $(A-C)_1$ less than 8, but of these, 12 were the infants of mothers with probable placental dysfunction. Two of these infants (both of diabetic mothers) scored 7 at 5 min. The remaining six infants were delivered of mothers assumed to have normal placental function. There were 112 patients in this group. The six individual $(A-C)_1$ scores were: 7, 5, 4, 4, 3 and 1. The 5-min $(A-C)$ scores of four of this group of infants was 8, and the remaining two scored 7.

Consideration of the induction–delivery interval is unlikely to be relevant to the condition of the neonate delivered under extradural analgesia. However, the time which elapses between the first incision to the myometrium and completion of delivery (the U–D interval) should be relevant if the postulates to explain the significance of this interval to neonatal well-being when general anaesthesia is used are correct (Crawford et al., 1976). The mean duration of the U–D interval exceeded 90 s in 19 of the 112 normal patients (group A elective sections). This is almost identical to the frequency (15.4%) reported for group A elective sections conducted under general anaesthesia (Crawford et al., 1976). However, only one (5.3%) of the 19 neonates subjected to a U–D interval of more than 90 s failed to achieve maximum $(A-C)$ scores. Of the 93 infants who had been subjected to a U–D interval of less than 90 s, five (5.4%) failed to achieve a maximum score.

There were three sets of twins in the series of elective sections, and one set in the emergency series. All six infants in the series of elective sections were in good condition at delivery.

DISCUSSION

The modifications in technique introduced into our practice since 1977 were based largely upon advice from Moir (1979). These have reduced considerably the frequency of undesirable features of this procedure. The number of patients who required supplementary analgesia or general anaesthesia with the previous technique was small, but there were undoubtedly several patients who were uncomfortable during the operation, but not sufficiently so to persuade the anaesthetist to administer i.v. or inhalation analgesia. Even with the present technique, some mothers become sufficiently anxious, bored or restless after delivery to require some sedation such as diazepam 5 mg i.v.

Maternal hypotension is unusual if the technique of incremental dosage—subsequent to fluid preloading—is adopted, and care is taken to avoid aorto–caval compression. The administration of a vasopressor is rarely required. This may be contrasted with the frequency of hypotension in two recently reported series in which bupivacaine was administered as a single dose. In one (Fox et al., 1979), nine of the 20 patients required ephedrine; in the second (Downing, Houlton and Barclay, 1979) 10 of 32 patients developed a significant decrease in arterial pressure, although only one required a vasopressor.

Occasionally bradycardia occurs. In this series it almost invariably occurred shortly after delivery and was probably induced by oxytocin. It was successfully treated by atropine i.v.

There is growing agreement that where there is no evidence of placental dysfunction, there is little difference in Apgar scores and acid–base results between infants delivered under extradural block and those whose mothers were given general anaesthesia (James et al., 1977; Downing, Houlton and Barclay, 1979; Fox et al., 1979). Although Downing and colleagues (1979) reported that the degree of metabolic acidosis of the neonate increased significantly with increase in the U–D interval, in the present series the U–D interval was not related to the Apgar minus colour scores. This contrasts with deliveries conducted under general anaesthesia (Crawford et al., 1976). It is possible that, when conducting a Caesarean section under extradural analgesia, the obstetrician tends to be more gentle and restrained in his manipulations, and that there is less disturbance of the placental blood supply during the period between incision into the myometrium and delivery of the infant.

The two main features which have inhibited greater use of extradural analgesia for Caesarean section have been obstetric wariness and the time taken to prepare the patient. Some obstetricians have an initial reluctance to operating upon an awake patient. This is difficult to understand, because of all surgical specialists the obstetricians are those who most frequently employ their manipulative skills upon patients with whom they can concurrently converse. These restraints can be overcome only by gentle persuasion continuously applied, and by reference to the examples of colleagues in the same hospital. One objection advanced has been that a potentially difficult section should weigh in favour of general anaesthesia. In our experience this is applicable only if the difficulty likely to be encountered is severe haemorrhage from an anterior low-lying placenta. If the myometrium is scarred—as, for example, from one or more previous sections—the choice of extradural block is advantageous since it reduces the insult which a prolonged induction–delivery interval and U–D interval would otherwise offer to the infant, and yet affords no increased hazard to the mother. Many of the cases referred to in this report were repeat sections.

The other objection is equally misplaced. It is true that if a successful block is to be ensured a considerable time will be spent in achieving it. This should cause no difficulty in an obstetric unit the standards of which meet the requirements for an extradural service. Few obstetric units in the United Kingdom conduct an average of more than one or two elective Caesarean sections per day, and there is no need to hurry the start of these. Most sections in such units will be performed by residents who have other duties in the delivery suite with which to fill in the waiting period. In this series, the occasions when the time from beginning the extradural block to delivery of the infant was more than 1 h occurred when an emergency intervened and the operation had to be delayed. The anaesthetist also is not unduly withdrawn from other routine work in the delivery suite, provided that there is a competent midwife available to supervise the care of the mother whilst the block is being established. The degree of urgency to conduct an emergency section must be an important factor in deciding whether or not the operation should be conducted under an extradural block. The choice will obviously be influenced in favour of a block if one is already in progress for pain relief in labour.

A list of the indications and contraindications is not germane to this discussion, but as in the use of extradural analgesia for labour, the contraindications diminish with increasing experience in an obstetric unit.

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EXPERIENCES AVEC L'ANALGESIE LOMBAIRE EXTRADURALE POUR LES OPERATIONS CESARIENNES

RESUME

On expose dans ce document les résultats de 324 opérations césariennes effectuées sous blocage lombaire extradural. Outre une précharge effectuée à l'aide de liquide administré par voie intraveineuse et l'abstention de compression aorto-veine cave, les modifications les plus récentes ont consisté à administrer de le bupivacaïne en doses croissantes, afin de moins se préoccupier de l'importance de la dose

totale et pour donner à la mère un supplément d'oxygéne jusqu'à l'accouchement. Par suite de ces modifications, la fréquence des malaises maternels et d'hypotension s'est trouvée diminuée et il est rare que l'on doive faire appel à une analgésie supplémentaire ou utiliser un agent vasopressif; l'administration de dizaépam après l'accouchement reste occasionnellement recommandable. La technique présente de nombreux avantages pour la mère et pour l'enfant et avec un bon service d'obstétrique, il y a peu d'inconvénients. La prolongation de l'intervalle entre l'incision du myomètre et l'accouchement semble être moins préjudiciable à l'enfant que lorsqu'on utilise une anesthesié générale.

ERFAHRUNGEN MIT EXTRADURALER LUMBARANALGESIE BEI KAISERSCHNITT

ZUSAMMENFASSUNG

Diskutiert werden die Resultate von 324 Kaiserschnitt-Operationen unter extraduraler Lumbarblockierung. Zusätzlich zu Vorbehandlung mit intravenos gegebener Flüssigkeit und der Vermeidung einer Aorta-Hohlvenen-Kompression gehorte es zu den neueren Modifikationen, stufenweise Bupivacain zu verabreichen, um nicht zu sehr die Gesamtdosis-Grösse berucksichtigen zu müssen, und die Mutter bis zur Geburt mit zusätzlichem Sauerstoff zu versorgen. Als Resultat kam es zu einer Reduzierung der Häufigkeit von Unbehagen und Hypotension bei der Mutter, und die Notwendigkeit für zusätzliche Analgesie oder Kreislaufmittel war selten. Die Verabreichung von Diazepam nach der Geburt ist gelegentlich immer noch ratsam. Die Methode hat viele Vorteile fur Mutter und Kind und wenig Nachteile bei guter Geburtshilfequalität. Die Verlängerung des Intervalls zwischen dem Einschnitt in das Myometrium und der Geburt ist fur das Kind weniger schadlich als die Verwendung von Lokalanasthesie.

EXPERIMENTOS CON ANALGESIA EXTRADURAL LUMBAR EN OPERACION CESAREA

SUMARIO

Se trata de los resultados de 324 operaciones cesáreas efectuadas bajo bloqueo extradural lumbar. Fuera de la carga previa con fluido i.v. y la eliminación de la compresión aorto-caval, las recientes modificaciones tienden a administrar bupivacaina en dosis incrementales sin preocuparse tanto de la importancia de la dosis total y a suministrar a la madre oxígeno adicional hasta el parto. El resultado de dichas modificaciones fue de reducir la frecuencia de la hipotensión y del malestar de la madre y la necesidad de una analgesia complementaria o de un vasopresor se volvió una rareza. La administración de diazepam después del parto es aconsejable todavía en algunas oportunidades. Esta técnica tiene muchas ventajas tanto para la madre como para el recién nacido y con un buen servicio obstétrico, muy pocas desventajas. La prolongación del intervalo entre la incisión del miometrio y el parto parece ser menos perjudicial para el recién nacido que cuando se administra una anestesia general.

Br. J. Anaesth. (1980), **52**, 827

EXTRADURAL BLOCK IN PATIENTS WHO HAVE PREVIOUSLY UNDERGONE CAESAREAN SECTION

C. Carlsson, G. Nybell-Lindahl and I. Ingemarsson

SUMMARY

In 119 patients who had undergone previous Caesarean section lumbar extradural block was administered to 77 (65%); the other 42 (35%) received analgesia with ketobemidone 0.8–1.0 ml i.m. or nitrous oxide in oxygen intermittently, or both. Controlled i.v. infusion of oxytocin for induction or acceleration of labour was given to 77% in the extradural group and to 40% in the other group. In both groups 88% were delivered per vaginam. In two patients the uterine scar ruptured; both had received oxytocin during extradural block.

The use of extradural analgesia in patients who have previously undergone Caesarean section is controversial (Albright, 1978; Bromage, 1978). Because of an increase in the Caesarean section rate (Hibbard, 1976; Johnell, Östberg and Wåhlstrand, 1976) it is important to define the risk precisely, particularly since extradural analgesia may offset the likelihood of further Caesarean section.

This is a retrospective report of the outcome in 119 patients who had undergone Caesarean section previously, in the majority of whom extradural analgesia was afforded.

PATIENTS AND METHODS

During January 1977–June 1979, 8041 women were delivered at the University Hospital, Lund, Sweden. In this period, 119 patients with a previous history of Caesarean section and who were again in labour were studied. If no specific contraindication existed, the patient's preference in respect of analgesia was allowed. Extradural block was given to 77 (65%); 42 (35%) received ketobemidone 0.8–1.0 ml i.m. or nitrous oxide in oxygen intermittently, or both.

There were various reasons for the previous Caesarean section; intrapartum fetal asphyxia and slow progress of labour predominated. The frequency of the indications did not differ between the two groups. In no case was contracted pelvis the reason for operation. All Caesarean sections were performed through a low transverse uterine incision.

Eighty-five per cent of the patients in the extradural group and 69% in the other group had undergone emergency Caesarean section (table I). Complications following surgery (wound infection and haematoma, parametritis and endometritis) had occurred in 27% in the extradural group and in 17% in the other group. In 86% and 76%, respectively, the patients had not previously experienced vaginal delivery.

TABLE I. *Description of the* 119 *patients*

	Extradural analgesia ($n = 77$)	Conventional analgesia ($n = 42$)
Age (yr)		
Range	23–36	22–39
Mean	29.6	28.3
Previous Caesarean section		
Emergency	65 (84%)	29 (69%)
Elective	12 (16%)	13 (31%)
Postoperative complications	21 (27%)	7 (17%)
No previous vaginal delivery	66 (86%)	32 (76%)

When the cervix was dilated to 4 cm (mean), the extradural block was performed. The extradural space was entered with a Tuohy needle between L2–L3 *or* L3–L4. A catheter was inserted and advanced 4–5 cm. Bupivacaine 0.25% 6–8 ml was administered initially. Repeat doses were given when pain recurred. Arterial pressure was measured regularly during the first 20 min after blockade. No vasopressor drugs were given but, as a precaution against hypotension, an i.v. infusion of approximately 200 ml of buffered saline solution was given.

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0007-0912/80/080827-04 $01.00

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All patients were monitored with cardiotocography (Hewlett–Packard 8030 A). Fetal heart rate was recorded by scalp electrode.

Uterine activity was recorded by means of an open-end catheter connected to a pressure transducer (Hewlett–Packard 1280 B). Blood samples from the fetal scalp for pH measurement were taken when fetal distress was suspected.

Oxytocin was administered as an i.v. infusion using an IVAC 501 (AGA, Sweden) infusion pump.

The Apgar score was recorded at 1, 5 and 10 min in every infant.

RESULTS

Extradural group (*table II*)

Oxytocin was given to 59 of the 77 patients (77%). Of these, labour was induced in 25; in 34, spontaneous labour was accelerated.

In this group, recording of intrauterine pressure was planned for all patients. In 62 (81%), a catheter was inserted; in the other 15, there were technical problems.

Satisfactory analgesia was reported by 73 of 77 patients.

The total mean duration of labour in patients with a spontaneous labour was 6.8 h. Extradural block was performed after a mean time of 3.8 h. In patients receiving oxytocin the corresponding figures were 11.4 and 5.8 h.

Sixty-eight patients (88%) were delivered by the vaginal route. Instrumental delivery (forceps or vacuum extractor) was performed in 25 (37%). Nine (12%) underwent Caesarean section because of slow progress (five), fetal distress (two) or suspected scar rupture (two). These last two patients complained of continuous pain and tenderness over the lower uterine segment. At operation, early signs of a ruptured scar were found, but the membranes were intact.

The Apgar score was less than 7 in four infants at 1 min, in none at 5 min.

Conventional analgesia (*table II*)

Oxytocin was administered to 17 (40%) of the 42 patients. Labour was induced in four and accelerated in 13.

Intrauterine pressure was recorded with a catheter in 18 patients.

The mean duration of labour was 6.5 h in patients with spontaneous labour and 8.6 h in those receiving oxytocin.

Vaginal delivery occurred in 37 patients (88%). In four of these instruments were used. In five (12%) Caesarean section was performed because of slow progress (four) or fetal distress (one).

Two babies had an Apgar score less than 7 at 1 min but none at 5 min.

DISCUSSION

Despite a longer duration of labour 88% of the patients receiving extradural block had a vaginal delivery, a figure identical to the other group. On the other hand, the frequency of outlet extractions was greater in the extradural group.

Published accounts of nerve block analgesia in the presence of a uterine scar have been predominantly case reports. Meehan, Moolgaoker and Stallworthy (1972) reported 75 patients in labour during caudal analgesia after previous major uterine surgery. Seventy of 75 patients had a vaginal delivery, only two spontaneously. Twenty-five (33%) had oxytocin stimulation during labour. In addition, Dr J. S

TABLE II. *Duration of labour (mean ± SD) and outcome of delivery in 119 patients with a previous Caesarean section. Figures denote no. of patients unless stated otherwise*

	Extradural block (77)		Conventional analgesia (42)	
	Spontaneous labour 18 (23%)	Oxytocin stimulation 59 (77%)	Spontaneous labour 25 (60%)	Oxytocin stimulation 17 (40%)
Duration of labour (h)	6.8 ± 2.8	11.4 ± 3.9	6.5 ± 3.1	8.6 ± 2.8
Duration of labour before the block (h)	3.8 ± 2.0	5.8 ± 3.2	—	—
Vaginal delivery	17	51	24	13
Spontaneous delivery	12	31	21	12
Instrumental delivery	5	20	3	1
Caesarean section	1	8	1	4
Scar rupture	0	2	0	0

Crawford (personal communication) had experience of a larger series of such patients.

Vaginal delivery after a previous Caesarean section could be hazardous because of the risk of scar rupture, regardless of the mode of analgesia. Such women in labour have been considered relatively unsuited to extradural block, as pain from the scar indicating threatened rupture could be obtunded (Albright, 1978). In our series there were two cases of scar rupture, both in the extradural group and receiving oxytocin. This combination was also associated with a long duration of labour and high frequency of instrumental delivery. Both patients exhibited classic symptoms despite the block. This "breakthrough" of pain within the blocked area was also found by Crawford (1976). Meehan, Moolgaoker and Stallworthy (1972) reported a similar frequency of scar rupture; these were found incidentally.

Scar dehiscence might be accompanied by abnormally located pain in the presence of a satisfactory extradural block (Eckstein, Oberlander and Marx, 1973), as is illustrated by a case of ours occurring after our study was ended. A 28-yr-old woman at term, who had undergone previous Caesarean section, received an extradural block during labour. After 2 h, she complained of pain in the upper left abdomen not affected by repeat extradural injection. There was no pain or tenderness in the scar area. Caesarean section was performed because of fetal distress. At the operation, total scar rupture with broken membranes was found. Mother and child recovered without complications.

Patients in labour after a previous Caesarean section must be monitored with special care. Cardiotocography and intrauterine catheterization are particularly valuable. Another measure is uterine palpation during labour (Meehan, Moolgaoker and Stallworthy, 1972). The high frequency of satisfactory analgesia and vaginal delivery in our extradural group suggests that extradural analgesia may be given to these patients provided that experience in the method and satisfactory monitoring of mother and fetus are available. However, care must be exercised if oxytocin is infused.

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BLOCAGE EXTRADURAL SUR DES PATIENTES AYANT SUBI ANTERIEUREMENT UNE OPERATION CESARIENNE

RESUME

Sur 119 patientes qui avaient antérieurement subi une opération césarienne, on a administré un blocage lombaire extradural à 77 d'entre-elles (65%), alors que les 42 autres (35%) ont reçu une analgésie à l'aide de kétobémidone à raison de 0,8–1 ml, administré par voie intramusculaire ou de protoxyde d'azote dans de l'oxygène administré d'une manière intermittente, ou encore les deux. L'administration contrôlée d'une infusion d'oxytocine pour l'induction ou l'accélération du travail a été donnée par voie intraveineuse à 77% du groupe extradural et à 40% de l'autre groupe. Dans les deux groupes, 88% des patientes ont accouché par voie vaginale. Sur deux d'entre-elles, il y a eu rupture de la cicatrice de l'utérus; toutes les deux avaient reçu de l'oxytocine pendant le blocage extradural.

EXTRADURALE BLOCKIERUNG BEI PATIENTINNEN NACH KAISERSCHNITT

ZUSAMMENFASSUNG

Bei 119 Patientinnen wurde nach einem Kaiserschnitt eine lumbare extradurale Blockierung verabreicht (bei 77, also bei 65%), während die anderen 42 (35%) Schmerzlinderung durch Ketobemidon 0,8–1,0 ml intramuskulär, oder intermittierend durch Stickoxyd in Sauerstoff, oder durch beides erhielten. Siebenundsiebzig Prozent der Patientinnen in der extraduralen Gruppe und 40% in der anderen Gruppe erhielten ein intravenöse Infusion von Oxytocin zur Einleitung oder Beschleunigung der Wehen. In beiden Gruppen kam es bei 88% zu Geburten per vaginam. Bei 2 Patientinnen kam es zu Rissen der alten Uterus-Kaiserschnittnarben; beide hatten während der extraduralen Blockierung Oxytocin erhalten.

BLOQUEO EXTRADURAL EN PACIENTES QUE HAN SUFRIDO CON ANTERIORIDAD CORTES DE CESAREA

SUMARIO

De 119 pacientes que habían sufrido con anterioridad corte de cesárea, se administró bloqueo extradural de la zona

lumbar a 77 (65%), las 42 restantes (35%) recibieron analgesia mediante ketobemidona, 0,8–1,0 ml, intramuscular o óxido nitroso en oxígeno de forma intermitente, o ambos. Al 77% del grupo extradural se le administró infusión intravenosa y controlada de oxitocín para la inducción o aceleración del parto, al igual que al 40% del otro grupo. El 88% de ambos grupos parieron per vaginam. En dos de las pacientes se abrió la cicatriz del útero; ambas habían recibido oxitocín durante el bloqueo extradural.

Br. J. Anaesth. (1980), **52**, 831

EXTRAPYRAMIDAL SYNDROMES AFTER PREMEDICATION WITH DROPERIDOL IN CHILDREN

L. J. Dupre and P. Stieglitz

SUMMARY

Four cases of extrapyramidal hypertonic syndrome were observed in 82 children who had been premedicated with small i.m. doses of droperidol. The frequency, time of onset, clinical description and treatment of this complication are discussed.

The use of droperidol for premedication in children provides good sedation, facilitates venepuncture and produces a potent anti-emetic effect. The extrapyramidal syndrome, although rare, is one of the disadvantages of this drug. This paper reports four cases of this syndrome, observed by the authors during 1 year.

CASE REPORTS

Patient No. 1

A 6-month-old boy was premedicated with atropine and droperidol 0.1 mg kg^{-1} for removal of stitches following repair of cleft lip. Forty-five minutes later, an akinetic hypertonic syndrome with lead pipe rigidity began to occur. This developed in successive periods of about 10 min over the next 6 h. Anaesthesia was not induced. After 6 h, an i.m. injection of chlorpromazine 0.4 mg kg^{-1} successfully treated the hypertonic syndrome. A previous anaesthesic had been given using halothane and pentazocine following premedication with atropine and alimemazine (Théralène) without incident. The child was anaesthetized uneventfully 6 months later with halothane after receiving a premedication of atropine and alimemazine.

Patient No. 2

A 7-yr-old girl underwent surgery for an abscess of the cheek. After premedication with atropine and droperidol 0.1 mg kg^{-1}, anaesthesia progressed normally with enflurane. Recovery was rapid. Eight hours later a hypertonic syndrome was noted, presenting as paroxysms characterized by opisthotonos, trismus, lateral flexion of the neck and oculogyric spasms. Consciousness did not seem to be impaired. After 2 h an i.m. injection of alimemazine 0.3 mg kg^{-1} was given to treat the crisis. During the past 3 months, the child underwent several anaesthetics without incident. The last operation was performed under neuroleptanaesthesia after premedication with atropine and droperidol 0.1 mg kg^{-1}. Another anaesthetic was given 2 months later using thiopentone and enflurane, after premedication with atropine and diazepam 0.2 mg kg^{-1}.

Patient No. 3

A 13-yr-old boy was given an i.m. premedication of atropine and droperidol 0.17 mg kg^{-1} before a cisternal puncture. Nine hours after the injection, a hypertonic syndrome identical to that in patient No. 2 occurred. It was characterized by opisthotonos, lateral flexion of the neck, trismus and oculogyric spasms. As the syndrome was still evident after 1 h, an i.m. injection of diazepam 0.17 mg kg^{-1} successfully treated the crisis. The child, who had been injured in a traffic accident 1 month before, had already undergone surgery twice under neuroleptanaesthesia after premedication with atropine and alimemazine 1 mg kg^{-1}. No particular signs were noticed apart from those associated with his injury (complex cranio-facial trauma). The day before, he had been premedicated with droperidol 0.17 mg kg^{-1} for a lumbar puncture and no hypertonic syndrome had been observed.

Patient No. 4

A 10-yr-old boy was anaesthetized with thiopentone and halothane for treatment of a dental cyst. He was premedicated with atropine and droperidol 0.16 mg kg^{-1}. The operation took place normally and recovery was satisfactory. Fourteen hours after premedication, a hypertonic syndrome became evident with opisthotonos, lateral flexion of the neck, trismus and oculogyric spasms. The child responded to suggestion. After 1 h an i.m. injection of diazepam

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0007-0912/80/080831-03 $01.00

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0.16 mg kg^{-1} treated the crisis. The patient's history did not indicate any previous illness.

DISCUSSION

During the year 1976, 82 children in our hospital were premedicated with droperidol before various operations on the head and neck and, in four, hypertonic syndrome was reported. The frequency of this complication seems to vary in paediatric anaesthesia. Davies and Doughty (1971) recorded no cases in a series of 240 premedications with droperidol 0.22 mg kg^{-1}. Grokhovsky and Gorchinskaya (1972) reported 11 cases out of 127 neuroleptanaesthetic procedures, and Gounot, Metafiot and Lambert (1976) two cases out of 104 similar anaesthetics.

Among neurolept-induced dyskinesias, Laplane and Dordain (1970) distinguished four groups:

(1) An akinetic syndrome with mask-like facies, decreased movement and lethargy.

(2) A hypertonic syndrome with plastic "lead pipe rigidity".

(3) Akathisia syndrome with inability to sit still and restlessness. Morrisson, Clarke and Dundee (1970) noted this fact in 30–45% of their patients.

(4) Dyskinetic syndrome (patients Nos 2, 3, 4),which is the most frequent. It affects mainly the facial region with trismus, movements of the tongue and lips, but never involves upper facial nerve distribution. It combines oculogyric spasms (American College of Neuropsychopharmacology, 1973) wry neck, opisthotonos and sometimes leads to "rotary" crisis as in the report by Debray and Galland (1970). Occasionally it occurs as a vegetative episode, with tachypnoea, sweating and vasodilatation. The syndrome develops through a crisis of 2–10 min duration, occurring more or less regularly. Suggestion may occasionally stop the crisis, but only temporarily.

Transition forms or combinations of these groups may occur, as in patient No. 1 who developed an akineto–hypertonic syndrome.

The patient recovers spontaneously without sequelae. However, the duration of the syndrome is not predictable. In cases of acute episode, the crisis does not last more than a few hours, but prolonged syndromes have been reported lasting for 6 years (Kurland, 1967).

According to Kurland (1967) there is a predisposing factor, since such syndromes are more frequent in patients suffering from Parkinson's diseases. Sex has no influence. Children are more susceptible to the effects of butyrophenones. In acute intoxication with droperidol, hypertonicity does seem to be related to dose. It occurs even with low dosage as used in this series of less than 0.2 mg kg^{-1}.

In addition to butyrophenones, some other neuroleptics, anti-emetics such as thiethylperazine, or metoclopramide (Brunet and Thiroloix, 1972) may induce such crises. The lapse of time between a single injection and the crisis is very variable. It may be only a few minutes after i.v. injection according to Janis (1972) and Clifton (1975), or more than 12 h after i.m. injection as in patient No. 4 presented here. In this child no evidence was found for reduction in the rate of metabolism of droperidol.

Ayd (1961) reports that this reaction has been misdiagnosed as seizure, tetanus, meningitis, encephalitis and poliomyelitis, resulting in emergency admission to hospital, spinal punctures, antibiotic therapy and even tracheotomy.

The treatment of this condition varied according to the authors. Grokhovsky and Gorchinskaya (1972) used atropine, while Laplane and Dordain (1970) used trihexyphenidyl. Debray and Galland (1970) administered a "sedative" neuroleptic such as alimemazine, promethazine or chlorpromazine. We used diazepam in patients Nos 3 and 4, relying upon the effects of suggestion and upon the sedative effect of diazepam. We were satisfied with this treatment.

On the whole, the occurrence of such reactions appears to be quite unpredictable even with small doses of droperidol. We have therefore decided to reduce the use of droperidol for premedication as much as possible in our anaesthetic practice.

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SYNDROMES EXTRAPYRAMIDAUX APRES PREMEDICATION AU DROPERIDOL SUR DES ENFANTS

RESUME

Quatre cas de syndromes extrapyramidaux hypertoniques ont été observés sur 82 enfants auxquels on avait administré de petites doses intramusculaires de dropéridol à titre de prémédication. On expose dans cet article la fréquence, le départ de réaction, la description clinique et le traitement de cette complication.

EXTRAPYRAMIDAL-SYNDROME BEI KINDERN NACH VORBEHANDLUNG MIT DROPERIDOL

ZUSAMMENFASSUNG

Vier Fälle hypertonischer Extrapyramidal-Syndrome wurden bei 82 Kindern beobachet, die mit kleinen Dosen intramuskulär verabreichten Droperidols vorbehandelt worden waren. Haufigkeit, Eintrittszeit, klinische Beschreibung und Behandlung dieser Komplikation werden diskutiert.

SINDROMES EXTRAPIRAMIDALES DESPUES DE PREMEDICATION CON DROPERIDOL EN NINOS

SUMARIO

Se notó cuatro casos de síndromes extrapiramidales en 82 niños que habían recibido premedicación con pequeñas dosis i.m. de droperidol. Se discute de la frequencia, tiempo de manifestación, descripción clínica y tratamiento de dicha complicación.

Br. J. Anaesth. (1980), **52**, 835

A PREVIOUS HISTORY OF ACUTE INTERMITTENT PORPHYRIA AS A COMPLICATION OF OBSTETRIC ANAESTHESIA

S. C. ALLEN AND G. A. D. REES

SUMMARY

The administration of general anaesthesia for Caesarean section is described in a patient with an established biochemical diagnosis of acute intermittent porphyria. The technique used did not precipitate an acute exacerbation of the disease. Drugs associated with obstetric care are considered in the context of their use in porphyria.

The problems of general anaesthesia associated with porphyria are well recognized, but the association of pregnancy and porphyria is rare. We describe the successful anaesthetic and analgesic management of a patient with acute intermittent porphyria who required Caesarean section.

Case history

Eight years before becoming pregnant, the patient, then aged 24 yr, was admitted to hospital with a history of prolonged intermittent abdominal pain. After initial conservative management, an exploratory laparotomy was performed with a presumptive clinical diagnosis of an appendix abscess. Thiopentone, suxamethonium, tubocurarine and halothane were used for anaesthesia. No problems were noted. Abdominal pain continued after the inconclusive laparotomy and narcotic analgesics were required. No organic cause for the pain was found and a psychiatrist's opinion was sought. Symptoms subsided after 14 days and the patient was discharged from hospital.

A clinical and biochemical diagnosis of acute intermittent porphyria was not made until 2 months later when the patient was re-admitted with abdominal pain, tachycardia, neuropathy and severe myopathy involving the respiratory muscles. Two milder episodes occurred in the next 18 months. No precipitating factor was identified to account for each acute attack.

Eight years after her first attack, the patient presented in the antenatal clinic at 8 weeks gestation. She had remained well since her last acute attack 6 years previously. The arterial pressure was 120/80 mm Hg. The pregnancy was uneventful until 34 weeks when hypertension and proteinuria were noted. Arterial pressure was 150/90 mm Hg. Pre-eclampsia worsened despite hospital admission with a maximum arterial pressure of 170/120 mm Hg. An elective Caesarean section was planned at 37 weeks gestation because of the severe pre-eclampsia. Hypertension had remained at 160/110 mm Hg. Serial estimations of urinary porphobilinogen were performed before delivery.

No premedication was given other than oral magnesium trisilicate mixture. Arterial pressure on arrival in the anaesthetic room was 160/105 mm Hg. After pre-oxygenation, anaesthesia was induced by inhalation using a mixture of 50% cyclopropane and 50% oxygen. Cricoid pressure was firmly applied as the patient lost consciousness. Suxamethonium 100 mg was given to facilitate rapid tracheal intubation. Tubocurarine 25 mg was given i.v. and the lungs were ventilated artificially with 50% nitrous oxide in oxygen and by 0.3–0.5% methoxyflurane. Immediately after delivery, pethidine 100 mg was given i.v. and the ventilating mixture was changed to 70% nitrous oxide in oxygen. Syntocinon 5 i.u. was given i.v., Hartmann's solution 500 ml followed by 5% dextrose 500 ml were given as i.v. fluid therapy. At the conclusion of the operation, residual neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg. The anaesthetic was uneventful, although the pre-existing hypertension persisted during anaesthesia.

A live female infant was delivered weighing 2560 g. Apgar scores were 4, 7 and 10 at 1, 5 and 10 min respectively. The infant had made vigorous efforts at breathing during delivery, causing inhalation of liquor and this was thought to have produced

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0007-0912/80/080835-04 $01.00

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the low Apgar score at 1 min. Anaesthesia was thought not to be a contributory factor.

After operation, progress was uneventful except for persistent hypertension. There were no clinical signs of an acute attack of porphyria and urinary porphobilinogen excretion was unchanged from values before the operation. Glucose solutions 10% were used to maintain a minimum input of 1200 calories daily until normal oral intake was resumed. On direct questioning of the patient 24 h after operation, there was no evidence of awareness during anaesthesia. The patient was able to go home on the 14th day after operation.

DISCUSSION

The association of acute intermittent porphyria and pregnancy is known to produce a high risk of acute attacks, probably because of the increase in maternal oestrogen production.

One survey (Hunter, 1971) showed a high overall mortality rate of 27%. A later survey (Brodie et al., 1977) stated that 54% of women with the disease who become pregnant had an acute attack during pregnancy or the puerperium. Previous knowledge of the diagnosis did not alter the attack rate, but the maternal mortality rate was only 2%. That report did not give details of the use of analgesics or anaesthesia. The difference in mortality rates might be explained by the comparatively rare use of barbiturates as sedatives in the treatment of pre-eclampsia in recent years. Acute intermittent porphyria is clearly a serious, though uncommon, complication of pregnancy.

In order to establish a biochemical diagnosis of an acute attack in the period after operation baseline values of porphobilinogen excretion in the period before operation are required in patients with known porphyria. In normal pregnant women, porphobilinogen excretion increases to a small extent in late pregnancy, but does not become abnormal (Lyberatos et al., 1972).

Problems of anaesthesia

Of the induction agents, propanidid is known to be safe. Althesin is also recommended as a safe induction agent by one standard text (Churchill-Davidson, 1978) although another clinical report (Wetterberg, 1976) and animal studies (Parikh and Moore, 1975) suggest that it is unsafe. Ketamine has opposing evidence from two animal studies as to its safety in porphyria (Parikh and Moore, 1975; Kostrzewska and Gregor, 1978). Direct comparison of these results is not possible since a different species was used in each case, and therefore interpretation of the evidence is difficult. However, its safe use in clinical practice has been shown twice in the same patient (Rizk, Jacobson and Silvay, 1977).

There are conflicting reports as to the safety of the volatile anaesthetic agents in relation to porphyria. Halothane was successfully used twice (Rizk, Jacobson and Silvay, 1977) and is also considered safe from animal studies (Parikh and Moore, 1978), but has been reported as unsafe elsewhere (Wetterberg, 1976). Another authority (Vickers, 1977) considers both halothane and methoxyflurane to be safe, but again animal studies suggest that methoxyflurane is unsafe (Parikh and Moore, 1978). Enflurane has similarly conflicting reports (Parikh and Moore, 1978; Stone and Munson, 1979).

The choice of drug is not easy in the presence of such confusing evidence. Indeed, it is well recognized that an acute attack may not be precipitated even when known porphyrogenic drugs are administered to patients with porphyria (Ward, 1965). It is also difficult to extrapolate directly the results of animal studies to the clinical situation.

Our choice of technique was based on the current evidence available. The choice of an induction agent was a difficult problem. Barbiturates being excluded, propanidid appeared to be the drug of choice, but it has disadvantages when used for Caesarean section (Mahomedy et al., 1976). Ketamine may produce neonatal depression in larger doses (Downing et al., 1976) and there is conflicting evidence about its use in porphyria. Ketamine also causes an increase in arterial pressure and this would be undesirable in pre-eclampsia (Meer, Downing and Coleman, 1973). Inhalation induction of anaesthesia with cyclopropane combined with cricoid pressure provided the rapid, safe induction necessary for obstetric anaesthesia. This technique was discussed before operation with the patient, who found it acceptable.

It is common practice to use a small concentration of a volatile anaesthetic agent as an adjuvant to 50% nitrous oxide in oxygen to ensure freedom from awareness before delivery. Trichloroethylene is an agent widely used for this purpose, but no reference to its use in porphyria could be found. Methoxyflurane was used at that time since it was believed to be safe. However, Parikh and Moore (1978) later published evidence in animals suggesting that it may be unsafe.

Caesarean section normally demands the use of an oxytocic drug. Ergometrine is contraindicated in porphyria (Wetterberg, 1976). Syntocinon is an acceptable alternative, particularly in a patient with hypertension, although there are no reports of its use in porphyria. Its use caused no problems in our patient.

Management after operation may require the use of analgesics and anti-emetics. I.m. pethidine (total dose 1200 mg over 72 h) was used for analgesia after operation. The safe use of metoclopramide in porphyria has been shown both by clinical use (Goldberg and McColl, 1978) and from studies in rats (K. McColl, personal communication). An anti-emetic was not necessary in our patient. Starvation is a known precipitating factor in porphyria. Dextrose solution 10% provided a suitable source of calories and fluid until oral intake was resumed.

The management of pre-eclampsia may require the use of sedatives. Barbiturates, although widely used in the past, are now contraindicated. Diazepam, given by bolus injection or as an infusion, is commonly used for sedation in pre-eclampsia. Animal studies (Parikh and Moore, 1978) suggest that it is safe, but there are two reports that its clinical use has precipitated an acute attack of porphyria (Wetterberg, 1976; Stone and Munson, 1979). Chlormethiazole infusion is increasingly used as i.v. sedation, but there are no reports in the literature as to its safety in porphyria. Hydrallazine is used as a hypotensive agent in pre-eclampsia, often in combination with diazepam, but the safe use of hydrallazine in porphyria has yet to be established. Pentolinium may be safely used as a hypotensive agent in porphyria (Katz and Kadis, 1973; Vickers, 1977). Chlorpromazine is known to be safe (Wetterberg, 1976; Vickers, 1977) and provides both sedation and hypotension and thus may be the drug of choice.

The use of local anaesthesia in porphyria is ill defined. Standard texts (Katz and Kadis, 1973; Atkinson and Rushman, 1977; Vickers, 1977; Churchill-Davidson, 1978) suggest that local anaesthesia should, for medico-legal reasons, be avoided in diseases where neurological symptoms may occur after operation and the local anaesthetic cannot be excluded as a causative factor. However, the safe use of extradural, caudal and pudendal blocks has been reported in porphyria (Tricomi and Baum, 1958; James, Rudolph and Abbott, 1961). If our patient had been allowed to deliver vaginally, we would have considered, if necessary, the use of extradural analgesia after consultation with the patient. General anaesthesia, however, was considered to be the most suitable technique for Caesarean section in this patient.

In the presence of conflicting reports on many drugs, it is not possible to make absolute statements on the safety of their use in porphyria. We would suggest, however, that the choice of drugs should be restricted to those indicated as being safe both by clinical case reports and by animal studies.

ACKNOWLEDGEMENT

We are grateful to Professor G. H. Elder, Biochemistry Department, University Hospital of Wales, for his interest and advice during the preparation of this manuscript.

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ANTECEDENTS DE PORPHYRIE INTERMITTENTE AIGUE—COMPLICATION D'UNE ANESTHESIE POUR OBSTETRIQUE

RESUME

On décrit dans cet article l'administration d'une anesthésie générale pour une opération césarienne effectuée sur une patiente ayant un diagnostic biochimique établi de porphyrie intermittente aigué. La technique utilisée n'a pas précipité l'exacerbation aigue de la maladie. Les médicaments et les soins obstétriques sont considérés dans le contexte de leur utilité dans les cas de porphyrie.

EINE KRANKENGESCHICHTE VON AKUTER INTERMITTIERENDER PORPHYRIE ALS KOMPLIKATION BEI GEBURTSHILFE-NARKOSE

ZUSAMMENFASSUNG

Die Verabreichung einer allgemeinen Narkose für Kaiserschnitt wird an einer Patientin beschrieben, bei der die biochemische Diagnose akuter intermittierender Porphyrie gestellt wurde. Die verwendete Methode fuhrte keine akute Verschlechterung der Krankheit herbei. Drogen, die in Geburtshilfefällen verwendet werden, werden im Zusammenhang mit ihrer Verwendung bei Porphyrie erwogen.

UN HISTORIAL PREVIO DE PORFIRIA INTERMITENTE Y AGUDA COMO RESULTADO DE UNA COMPLICACION EN LA ANESTESIA PARA OBSTETRICIA

SUMARIO

Se describe la administración de anestesia general para efectuar un corte de cesarea en una paciente con diagnosis bioquímica establecida de porfiria intermitente y aguda. La técnica empleada no precipitó una exacerbación aguda de la enfermedad. Las drogas asociadas con el cuidado de obstetricia se consideran dentro del contexto de su uso en el terreno de la porfiria.

Br. J. Anaesth. (1980), 52, 839

CORRESPONDENCE

HEPATOTOXICITY OF REPEATED INHALATION ANAESTHETICS

Sir,—The papers by Fee and others (1979) and McIlroy and others (1979) raise a number of points which have been dealt with elsewhere (Strunin, 1979, Editorial, 1980). It is important to answer the question: what do changes in the blood enzyme activities as studied by these authors indicate?

Of the enzymes measured, aspartate aminotransferase (AST), alkaline phosphatase (ALP) and lactic dehydrogenase (LDH) are widespread throughout the body, and changes cannot necessarily be said to have arisen from the liver. In the case of LDH, measurement of isoenzyme V would have provided more information on the release of the hepatic enzyme, but there is no indication that this was done. Alanine aminotransferase (ALT) is present to a greater per cent of its total body activity in the liver than the three enzymes already mentioned, but is still not liver-specific Gamma glutamyl transferase (GGT) is present in the kidney, liver, biliary tract and spleen. Although the hepatic content of the enzyme is *small* compared with that present in the kidney, the activity of this enzyme is increased in about 90% of all hepatic disorders, especially in hepatic obstructive jaundice, and this may have been the cause of increased GGT in some of the patients investigated.

is directed towards recognizing evidence of hepatocellular damage with consequent release into the blood stream of enzymes normally contained within hepatic cells. It would thus be better to look at enzymes which are solely present in the liver, or present elsewhere in very small concentrations, such as alcohol dehydrogenase, glucose-6-phosphatase, sorbitol dehydrogenase, xanthine oxidase and the enzymes of the urea cycle (Brohult, 1967; Cacciatore et al., 1974, Drotman and Lawhorn, 1978; Vassef, 1978; Dooley, Turnquist and Racich, 1979, McHale, Grimes and Coughlan, 1979)

Fee and colleagues also suggested that their results were in agreement with the comparative toxicity data obtained by Stacey, Priestley and Hall (1978) using isolated hepatocytes in suspension. As a model system, isolated hepatocytes exhibit many features similar to the intact organ. Our studies with some of the i.v. induction agents would suggest that this technique allows ready and easy assessment of comparative hepatotoxicity at clinical and toxicological concentrations (Sear and McGivan, 1979). Use of this system for other drugs has shown a high correlation between *in vitro* toxic effects and the occurrence of *in vivo* hepatic damage. However, the results of Stacey, Priestly and Hall (1978) on the toxicity of some of the volatile anaesthetic agents are misleading because of these authors' failure to consider the different partition coefficients of the four agents studied. They were therefore using different MAC ranges· for methoxyflurane up to 55 times MAC, and for enflurane up to 9 times MAC. Furthermore, at concentrations used, clinically, there was no evidence of hepatotoxicity in any of the four agents investigated.

Perhaps the results from the study of Fee and his colleagues may be viewed as possible evidence of hepatotoxicity from repeated halothane anaesthetics. However, the indices investigated were limited in their relevance and specificity, and can only provide data on one small aspect of liver pathophysiology.

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Sir,—Dr Sear suggests that for recognition of evidence of hepatocellular damage it would be better to measure enzymes which are present solely in the liver How pleasant it would be for clinical chemists and others if only they could do so with any degree of confidence! Anyone who has been interested in the study of liver function is, however, only too well aware of the repeated appearance of new enzyme tests of such function ever since Wróblewski introduced the concept of "biochemical biopsy" about 25 years ago, the vast majority have been discarded as useless after much intense and hopeful work had been done in the everyday world of the clinical chemistry laboratory. The existence even now of a number of "liver function tests" and the increasing interest in discriminant function analysis of their results only serve to emphasize the fact that there is no unique test of hepatocellular dysfunction which can be readily applied routinely to large numbers of specimens We accept the role of hepatocyte preparations as models for the investigation of the toxic effects of drugs; their use may serve as a valid screening procedure before *in vivo* tests, but will not detect the possibility of idiosyncratic reactions or determine the extent to which such factors as obesity, smoking or drug-taking may affect the condition of a patient's liver after anaesthesia.

Regarding some of the enzymes which Dr Sear puts forward as useful, the late J. H. Wilkinson, Inaugural President of the International Society of Clinical Enzymology, says (Wilkinson, 1976) that there have been few studies of the diagnostic possibilities of the serum activity of alcohol dehydrogenase, although one group of workers reported in 1968 that the test was a useful indicator of acute parenchymal liver damage; and that sorbitol dehydrogenase (of which the richest source is the liver, while some occurs in the prostate and kidney) is of limited use in diagnosis owing to its relative instability in serum, with the result that the finding of a normal activity does not exclude liver disease. These, and the other enzymes mentioned by Dr Sear, have obviously not yet been shown to be of great value in the study of liver dysfunction. Further, in discussing liver cell necrosis and abnormal membrane permeability, we find Rosalki (1976) stating that "aspartate transaminase may be elevated in several non-liver diseases (especially heart disease) whereas non-hepatic alanine transaminase elevation is unusual." Further support for our choice of enzymes could be quoted (Schmidt, 1978).

It would seem to be best to do as we have done; that is, to use those methods of testing which, whatever their shortcomings, are widely accepted as of proven value, and which can be readily applied under the conditions of a prospective study. There is a parallel in the diagnosis of diabetes: "it could be argued that undue diagnostic emphasis has been placed on blood glucose, in that many other aspects of metabolism are also deranged in diabetes, but no useful alternative diagnostic measure has yet emerged" (Keen, Jarrett and Alberti, 1979).

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LOCAL COMPLICATIONS OF THIOPENTONE

Sir,—I am interested to note that Dr Davies (1979) believes his figures indicate a reduced frequency in the local complications of thiopentone injection over the past few years. Unfortunately, his figures do not justify this conclusion because the extent of the use of thiopentone is not included in his article. While arguing that the gradual change from 5% solution to 2.5% solution has been welcomed by the Medical Defence Union and others, there is in fact no evidence presented here that this is responsible for the reduction in side-effects reports.

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KETAMINE REQUIREMENT IN CHILDREN

Sir,—Dr Russell (1979) described inadequate anaesthesia following ketamine. I would like to report a similar case in which the ketamine requirement was large.

A female child aged 14 weeks and weighing 3.2 kg presented with failure to thrive and inability to swallow; nasogastic tube-feeding was required. She had a ventricular septal defect. Mild heart failure was treated with digoxin and frusemide. An EMI scan showed a very large Dandy Walker cyst almost completely occupying the posterior fossa and pushing the brain upwards and forwards. There was dilatation of the lateral ventricles.

The cyst was drained via a Pudenz catheter into the peritoneal cavity. The child was premedicated with atropine 100 μg. Following an inhalation induction of anaesthesia with oxygen, nitrous oxide and halothane, tracheal intubation was facilitated with suxamethonium. Anaesthesia was maintained with nitrous oxide in oxygen. Alcuronium was given for IPPV and was antagonized with atropine and neostigmine. The procedure was entirely uneventful. However, on the following day a leak of cerebrospinal fluid from the scalp wound was noticed. This persisted, accompanied by collapsed fontanelles and the posterior fossa was re-opened 3 days later. By this time the child's general condition had deteriorated. The pulmonary plethora on the chest x-ray had increased and her weight had decreased to 3 kg. It was decided to use ketamine and 100% oxygen for anaesthesia. Premedication was with atropine. Ketamine 25 mg was administered i.m. and an i.v. cannula was inserted. Considerable movement occurred and four injections of ketamine 6 mg were given i.v. during the 15-min procedure. At operation the burr hole through which the catheter passed into the Dandy Walker cyst was filled with cyanoacrylate glue and the wound resutured.

The patient had received 49 mg of ketamine (25 mg i.m. and 24 mg i.v.). The posterior fossa lesion should not influence the dissociative analgesia produced by ketamine, although in this case the dilatation of the lateral ventricles may have had an effect. Dr Russell cites the report by Morse and Cave-Smith (1974) of successful ketamine anaesthesia in an infant with anencephaly. However, in both his and the present case it is likely that normal neural pathways between the limbic system and cortex may have been disturbed.

Lockhardt and Nelson (1974) studied the effect of age on ketamine requirement. Following atropine premedication ketamine 5 mg lb^{-1} was administered i.m. They found that i.v. supplementation was required to prevent limb movement before surgery in 70% of patients less than 1 year of age and showed that i.v. ketamine requirements for surgical anaesthesia were associated with age, weight and surface area, age being most significant:

i.v. ketamine ($\mu g\ lb^{-1}\ min^{-1}$) $= 70.4 - 11.5 \times$ age (yr)

Other authors have described an increased MAC value for halothane in this age group (Gregory, Eger and Munson, 1969; Nicodemus et al., 1969).

Alternative possibilities for the greater ketamine requirement of younger children include differences in cerebral blood flow and neuronal density, incomplete myelinization with impaired transmission, differences in cardiac output and larger extracellular fluid volumes. Regardless of the possibility of abnormal neuronal pathways within the brain, the ketamine requirement of young children should be expected to exceed that of adults.

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RESPIRATORY DEPRESSION AFTER EXTRADURAL MORPHINE

Sir,—The editorial by Spence (1980) advocates the use of extradural narcotics as a new and efficient method of relieving pain after operation. It also mentions the risk of inadvertent ventilatory depression from excessive doses of narcotics entering the spinal fluid. Magora and colleagues (1980) reported their experiences of extradural morphine 2–3 mg in 10 ml of 10% dextrose in 98 adult patients without any haemodynamic or respiratory complications.

Respiratory depression has been reported after the use of intrathecal morphine in both large (15 mg) (Liolios and Andersen, 1979) and smaller doses (3–5 mg) (Glynn et al., 1979), and after extradural pethidine 50–100 mg (Scott and McClure, 1979). It seems pertinent to report respiratory depression after extradural morphine 4 mg in 10 ml normal saline.

A healthy 83-yr-old man had no premedication before transurethral resection of the prostate gland; extradural analgesia was achieved with carbocaine injected through an extradural catheter inserted at L2–3. Postoperative analgesia was provided by morphine 4 mg in 10 ml normal saline administered through the catheter before it was removed shortly after the cessation of surgery. Six hours later, the patient was comatose with inadequate ventilation and pin-point pupils.

He responded to naloxone 0 4 mg i.v., his arterial P_{CO_2} changing from 13.0 to 6.9 kPa and P_{O_2} from 3.2 to 8.8 kPa. Three further doses of naloxone were given to maintain adequate ventilation during the following 4 h.

Ventilatory depression after extradural pethidine has been reported as occurring approximately 30 min after extradural administration (Scott and McClure, 1979). In contrast, the time of onset in the patient described was 6 h later, about the same time observed after intrathecal morphine: 6 h and 11 h (Glynn et al., 1979) and 7 h (Liolios and Andersen, 1979).

Prolonged observation of the patient may be required to detect late respiratory complications.

The safe limits of dosage and volume of extradural morphine are still to be defined. It would be interesting to know to what extent the age of the patient may influence these limits.

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OXYGEN TRANSPORT DURING DOPAMINE INFUSION

Sir,—Dr Scott and his colleagues (1979) contribute a potentially valuable paper on the effect of dopamine on whole body oxygen transport. However, their conclusions do not seem to be borne out by their data.

Oxygen and carbon dioxide production. Their increases in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were only significant after 60 min at the greater dose of dopamine (30 $\mu g\ kg^{-1}\ min^{-1}$) when compared with *initial control.* The smaller dose of dopamine produced no significant changes.

Oxygen availability and ratio. At no time was oxygen availability significantly changed compared with initial control, and the oxygen availability ratio did not change under any of the test conditions.

Their conclusion that dopamine increased oxygen delivery is not correct. Comparison with the post-dopamine state appears inappropriate as the haemodynamic and metabolic state is very different. Oxygen utilization only changed in one test condition and so any inferences about the relationship between oxygen transport and utilization are not possible.

I question the value of giving percentage changes when the absolute value of two control means are different. If we take the example of carbon dioxide production, a change from 4.9 to 7.30 represents a change of 49%. If the same absolute change (i.e. 2.4) had occurred from the other initial control of 6.0, then this would be a 40% change. Is the second change any less significant biologically than the first?

Last, the technique of comparing each of the means of each parameter one with another has a certain danger in it, as there is the possibility that apparently significant associations will appear by chance. The larger the number of means compared, the more likely this becomes.

J. H. Chamberlain
London

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MATERNAL MORTALITY AND ANAESTHESIA

Sir,—Dr Moir, in his editorial, Maternal Mortality and Anaesthesia, correctly emphasized the continuing problem of aspiration despite the use of antacids (Moir, 1980). He speculated that "... particles of magnesium trisilicate might be a pulmonary irritant". We examined the question in dogs (Gibbs, Schwartz et al., 1979). Kolantyl-Gel, an antacid preparation commercially available in U.S.A. was compared with hydrochloric acid; after instillation to the lung it produced comparably severe decreases in Pa_{O_2} and increases in pulmonary shunt. Histologically, the acid produced the expected haemorrhage, exudate and oedema, while the antacid produced severe bronchopneumonia that did not totally disappear within 1 month. Five other commonly used antacid preparations caused similar histological changes when introduced to the lungs of rabbits (Wynne, Gibbs and Hood, 1979). Magnesium trisilicate, the preparation most widely used in the United Kingdom, is likely to cause similar findings, since all these antacids are of the emulsion-type and contain a variety of globules and particles.

We compared subsequently the consequences of emulsion antacid with clear antacid sodium citrate 0.3 mol litre^{-1}. Although the physiological changes were similar, the pathological abnormalities were much less severe for the citrate aspirate (Gibbs, Hempling et al., 1979). Therefore, we are currently investigating the effectiveness of sodium citrate as an antacid, since we still believe that neutralization of gastric acid is a worthwhile objective. Finally, we have also shown that aspiration of partially digested food even at pH greater than 2.5 produces physiological, histological and x-ray derangements, at least as severe as those caused by hydrochloric acid at pH 1.8 (Schwartz et al., 1980). Acidification of foodstuff causes death in the same experimental model. These findings support Dr Moir's implication that aspiration of acid is not the sole cause of Mendelson's Syndrome.

Charles P. Gibbs
James W. Wynne
Florida, U.S.A.

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JOHANNESBURG A–D CIRCUIT SWITCH

Sir,—We have read with great interest the paper on the Johannesburg A–D circuit switch by Drs Manicom and Schoonbee (1979). They introduced the concept of combining in a single system the principles and advantages of the Mapleson A (Lack) system for spontaneous respiration and the Mapleson D (Bain) system for controlled ventilation.

Have Drs Manicom and Schoonbee considered the rebreathing that will occur with the new system during change-over from spontaneous to controlled ventilation or *vice versa*? At the moment of change-over the gases that *were* in the expiratory limb now become the gases that will be inspired at the next breath, causing an increase in FI_{CO_2}. The problem is exacerbated when the reservoir bag in the Mapleson D position becomes the reservoir bag in the Mapleson A position; in the former position it would contain up to 2 litre of expired gas.

In 20 anaesthetized patients the authors, while studying a similar system, investigated the effect of this rebreathing and found initial increases to 4% in FI_{CO_2} and 1% in FE'_{CO_2}, using a constant fresh gas flow of 70 ml kg^{-1} min^{-1}. It took more than 10 min for the effect of this rebreathing to be eliminated. In the healthy patient this would not be a hazard; in the seriously ill, it might be.

D. Humphrey
J. W. Downing
J. G. Brock-Utne
Durban, South Africa

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MUSCULAR PARALYSIS FOLLOWING I.V. REGIONAL SUXAMETHONIUM TEST

Sir,—Baraka (1978) administered regionally suxamethonium 5 mg i.v. for clinical studies on conscious patients with traumatic peripheral nerve lesions. A contraction of the denervated muscle took place with a painful cramp-like sensation. Systemically, the only sign observed was a mild ptosis following the release of the tourniquet. Baraka recommended the use of the i.v. regional suxamethonium test in conscious patients to confirm the diagnosis of nerve injury before suturing is attempted and as a diagnostic aid in other clinical situations.

Experimenting on himself, one of us (J. P.) used Baraka's method by injecting suxamethonium 5 mg diluted in normal saline 40 ml over a period of 30 s via an i.v indwelling cannula placed between the fourth and fifth metacarpal on the dorsum of the left hand. The arm was exsanguinated by elevation for a few minutes and a tourniquet was placed around the upper arm and inflated to 250 mm Hg. The tourniquet was released 3 min after the end of the injection.

In the area of the injection site cramp-like pain commenced a few seconds after the injection began and spread to the hypothenar eminence and ulnar flexor muscles, continued for about 15–20 s and disappeared during the course of the injection. In the region of the ulnar flexor muscles there was a pricking sensation and multiple, fine twitches were perceived These phenomena vanished before the tourniquet was released. During the occluded phase, all fingers could be moved voluntarily.

A few seconds following release of the tourniquet, double vision developed, the eyelids drooped, multiple painless, pricking sensations occurred in regions of the trunk, arms and calves and complete paralysis developed. Artificial ventilation of the lungs was performed for 6 min. The first sign of returning muscle activity was the ability to move the eyelids; 60 s later, sitting up was possible. At this time the muscles of the left forearm and hand were still completely paralysed. Only at 16 min following tourniquet release was the muscle force considered to have returned to normal. A distinct myalgia in movement of the neck and pharyngeal muscles and of the left hand and finger flexors existed, which disappeared gradually within the next 24 h.

The subject was 40 years old and healthy with the exception of an inclination to hyperuricaemia and was not receiving medication. Anaesthesia 2 years earlier, including the use of suxamethonium 100 mg following i.v. injection of diallylnortoxiferine 2 mg, had progressed normally. After the incident the following were recorded: pseudocholinesterase activity 106 u. ml^{-1} (normal: 80–120 u. ml^{-1}), dibucaine no. 70 (77–83).

This appeared to be an example of an unexpected hypersensitivity to suxamethonium 5 mg. Kalow and Lindsay (1956) have also observed some individuals who suffered profound paralysis and apnoea for 15 min after the same small dose. In view of the dibucaine number and the normal pseudocholinesterase activity we are not in a position to explain the incident. Probably the unusual behaviour of the extremity muscles studied after regional application (no neuromuscular blockade) and systemic spread of suxamethonium (muscular blockade) points to a humoral factor. Irrespective of the aetiology of the disturbance, the possibility of its occurrence suggests that the i.v regional suxamethonium test on conscious patients should be abandoned.

W. Schreiber
J. Plötz
Bamberg, Germany

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POSTERIOR INTERCOSTAL NERVE BLOCK

Sir,—I was interested to read the excellent description of posterior intercostal nerve block by Nunn and Slavin (1980) which demonstrated so well what we were aware of clinically when using a similar technique for thoracoplasty under local analgesia in the late 1940's. We used 0.5% procaine hydrochloride and later 0.5% and 0.25% lignocaine with adrenaline, injected slightly closer to the midline. When several needles were used it was quite common to see solution injected into the upper spaces appearing from the lower needles. The operation was unpleasant for the patient because he was only lightly sedated but became more sleepy as the local anaesthetic was absorbed. He could hear the ribs being resected and could not always avoid coughing during the apicolysis of the first stage, but the quality of analgesia was excellent. Several patients said to me that a thoracoplasty with this technique was preferable to bronchoscopy under local analgesia.

It is a welcome trend that some of the simple safe nerve blocks used in the pre-curare days (James, 1943) are now, with the long-acting drugs available, being combined with general anaesthesia to reduce pain after operation.

R. I. W. Ballantine
London

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ETOMIDATE

Sir,—In the recent article by Carlos and Innerarity (1979) about 20% of the patients studied reported pain on injection of etomidate into an antecubital vein.

My experience is quite different. I changed from using hand or forearm veins to the antecubital fossa in an attempt to reduce injection pain. In more than 100 patients, not one has reported pain. I note however, that the etomidate in the study was injected over 45 s, whilst my average injection time is less than 10 s. My usual premedication is oral diazepam with droperidol, and I precede the etomidate with fentanyl 1 $\mu\text{g kg}^{-1}$.

This routine has eliminated pain, and substantially reduced involuntary movement, leaving me with a highly satisfactory induction agent.

N. T. M. Jack
Winterswijk, Netherlands

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BOOK REVIEWS

The Parisian Education of an American Surgeon: Letters of Jonathan Mason Warren (1832–1835). With notes and introduction by Russell M. Jones. Published (1978) by the American Philosophical Society, Philadelphia. Pp. xiv+266; illustrated; indexed. Price $8.

The three commonly reproduced illustrations of the birth of general anaesthesia at the Massachusetts General Hospital, Boston, on October 16, 1846, all include not only the principals in the drama, the patient Gilbert Abbot, the anaesthetist W. T. G. Morton, and the surgeon John Collins Warren, but also, among others, Jacob Bigelow, Professor of materia medica at Harvard, whose letter to Dr Francis Boott took the news across the Atlantic, and Jonathan Mason Warren, the surgeon's son.

Jonathan Mason Warren was born in Boston into a surgical family in 1811. His father was the son and grandson of surgeons, and Mason, as he was known in the family, continued in the tradition. He began his studies at the Massachusetts Medical College, which later became the Harvard medical faculty, in 1829, and received his diploma in February 1832. A month later, shortly after his 21st birthday, with 40 pages of instructions from his father, he sailed for France, where he spent the next 3 years in advancing his medical and surgical studies; his father had studied in Europe between 1799 and 1801.

Mason's letters to his father, in which he described Parisian medicine and surgery, the celebrated physicians and surgeons, the hospitals, the operations, the instruments and the advances that were rapidly taking place, were preserved in the Warren Family Papers, and have recently been published by the American Philosophical Society, with annotations by a historian, Professor R. M. Jones.

Mason's letters paint a most vivid picture of the Parisian medical scene. He studied under or observed the work of such illustrious practitioners as Civiale and Sichel—pioneers respectively of lithotrity and ophthalmology—Dupuytren, Louis, Velpeau, Richerand, Denonvilliers, Cloquet, Roux and the great Larrey, regarded by that time as "an historical curiosity rather than a respected teacher". Through Paris also at this time, and recorded in Mason's letters, passed several of the figures better known to us from their activities some dozen years later; Charles Thomas Jackson, who was living in Paris when Mason arrived, and who initially took charge of him; Jacob Bigelow; Francis Boott of Gower Street; and Oliver Wendell Holmes, one of Mason's class-mates.

Mason had visited the United Kingdom *en route*, and had called on Sir Astley Cooper, Thomas Hodgkin, James Syme and Robert Liston. He returned to England when the teaching in Paris was in recess, and in one letter he summarizes his impression of the differences in attitude and practice between the two countries. "Paris at the present day offers I think much greater advantages for study than London from the great number of public hospitals and lectures and more particularly for the private courses which for certain branches must be very valuable. Their practice of medicine and surgery I think but little of. It seems to be more an object to study the natural history of disease and to perform an operation beautifully and quickly than to save the life of a patient. It is on this account that I think every student should see the English practice after studying in Paris as they are very apt to fall into the French mode of considering disease." Later, under the influence of the great clinician and morbid anatomist Louis, he concluded "Surgery as a science is undoubtedly far more advanced in England and America than in France whilst medicine, which we have always flattered ourselves under our English instructors, we were so enlightened, laughing in our sleeves at the French expectant practice, is now under the effort of Louis and his followers in a degree emerging from that cloudy and theoretical state which the English have never dared to enter. Keep the bowels open seems to be the great point in English practice, all other means being accessory."

Astonishingly major and lengthy operations were being performed, without the benefit of anaesthesia. Mason, who later made important contributions to the development of plastic and restorative surgery in the United States, was interested in the work of Dieffenbach, who had performed the operation of rhinoplasty on about 100 patients, creating a new nose by raising and shaping a pedicle flap from the forehead, a procedure which Mason describes in some detail. The surgical pathologist Marjolin, however, discouraged the operation. "He says *pour lui* he should prefer an artificial nose which are made so well in France as scarcely to be known and mentioned the case of a medical student with whom he dissected for 10 days without discovering his having anything unnatural and which he only finally discovered one day by the man being obliged to blow his nose suddenly seized the end, turned it to one side of his face, performed the operation and restored the member which moved on a kind of hinge to its natural position."

Bladder stone was still a common condition and a great problem, and battle raged between the lithotomists of various persuasions and the lithotritists, but the mortality rate from the closed operation was even greater than from the varieties of the open; by and large only those dismissed as unfit for operation survived.

"A hernia was beautifully operated by Roux the last week: the patient, however, as usual died." He is critical of Roux, who, he says "has gone to Italy leaving town the day after having completely quartered an old man of about 70 for a tumor of the shoulder joint on which Dupuytren had refused to operate. In general I avoid criticising the operations of great men who are often most unjustly attacked, but the operations of Roux depend entirely upon a desire to operate without the least consideration of the case, do not seem to me to be fair play. The present patient died an hour after, without the operation he would have probably lived 5 or 6 years longer bringing him up to the common age of man." Of amputations "Dupuytren says one out of two are saved, but many die after leaving the hospital worn out by the lengthy cure".

Mason gives an account of the illness and death of Dupuytren, who bestrode the Parisian medical scene like a Colossus. He describes a death from air embolism, and mentions the use of creosote, first distilled from pine tar in 1832, for the cauterization of ulcers. It was used also for several years as a wound dressing, which pre-Listerian practice is regularly rediscovered and publicized by surgeons who cannot know much of the history of their specialty. He is very concerned about his father's health, and on several occasions he mentions particularly "those troublesome local affections of the hands which seem to depend as much on exposure and rewashing as from irritant applications". Is this an indication that John Collins Warren attempted to render his hands more than socially clean before operating?

Mason describes cataract extractions, the repair of cleft palate, tonsillectomy, and a primitive form of dacryocystorhinostomy, all performed without anaesthesia. To amputate the cervix for carcinoma the uterus was pulled down until it projected from the vulva, a procedure which required about 15 minutes of steady traction by the surgeon's assistants. "The patient at times complained of great pain in the abdomen. She died the third day 48 hours after operation."

The letters have been transcribed and edited by Professor Jones, not without some difficulty, from the manuscript, which "suggested at times the tracks of a crab across sand"; and he has appended a most instructive introductory essay in which he describes the Parisian medical world of the 1830's, and illustrates some of its great hospitals and leading personages; he has also exhaustively and informatively annotated the text. One of the great pleasures of reading this book, apart from the almost tangible effect of immediacy that it creates, is that one is able to observe Mason's own development during his 3 years in Paris, from hesitant and uncertain beginnings, through a gradual increase in confidence and authority, until in his last letters his accounts, both descriptive and analytical, are most impressive.

Professor Jones reproduces a sketch of Mason, almost a caricature, drawn by a friend in 1834, and from it we can at least see that he was a stylish dresser. For his appearance in later years we must turn to the illustrations already mentioned; the most authentic is the daguerreotype reproduced by Dr Duncum in her *Development of Inhalation Anaesthesia*. The widely copied engraving by H. B. Hall, which first appeared in N. P. Price's *Trials of a Public Benefactor*, is wrongly labelled. Mason, now balding and moustached, stands immediately to the right of his father.

Although in paperback, the book is very well produced, and well worth binding. It is enthusiastically recommended; it is of the greatest interest to both anaesthetists and surgeons, and it adds a whole extra dimension to what we already know of the history of our specialty, and of those who assisted at its *accouchment*.

D. Zuck

Pediatric Anesthesia Handbook. By Richard M. Levin. Published (1980) by Medical Examination Publishing Co., Inc. Pp. 364; indexed; illustrated. Price $13.75.

This second edition of Dr Levin's book has appeared some considerable time after the original work and has been extensively expanded. The result is a "handbook" in which the information is presented in a condensed form with many headings and sub-headings. This format has been chosen in the belief that the reader will more quickly gain answers to the problems which are being faced, but the price for this decision is that the style is necessarily terse and opinions are dogmatic.

There are 10 sections and useful appendices at the end. The sections cover a very wide range of paediatric practice, from anatomical and physiological characteristics, evaluation before operation, pre- and postoperative care, the management of anaesthesia, special paediatric operations, special problems, associated diseases, respiratory therapy and cardiopulmonary resuscitation.

A great deal of valuable information is contained in the book and the manner of presentation makes it easy to gain an impression of the recommended techniques in Dr Levin's own practice. Naturally, there are aspects of practice with which individuals will disagree. The only point which may cause a British reader some irritation is in the nature of presentation and detail. For example, tracheal tube sizes are given in French gauge. Many illustrations are superfluous, for example figures 3.27–3.31, and it is a pity that a doll is used for demonstration rather than a real patient. It is quite surprising to find that some illustrations of questionable value are actually repeated, for example figures 4.5 and 4.6. Care with the illustrations seems to have been minimal and this detracts from the value of the information contained, for example figure 3.36 is published upside-down.

It was extremely disappointing to find that, although a section is devoted to "Respiratory therapy for the pediatric patient", it contained very little information useful to the practising anaesthetist In fact, the section on intermittent positive pressure breathing is totally inadequate and very unhelpful, especially as the author has seen fit to refer to another publication by himself as a means of coping with this area.

It was a further disappointment to find that the quality of the book was marred by the manner in which it is bound. After a reasonably careful perusal, the pages began to fall out and whole sections have detached themselves from a very inadequate and unstable form of binding at the spine of the book.

Despite these criticisms, there is much of value in this publication. It is to be recommended as a further addition to the sparse literature and used, essentially, as a means of obtaining an opinion on the background and some details of management that are involved in paediatric anaesthetic practice.

John Inkster

Anesthesia and the Patient with Heart Disease. Edited by Burnell R. Brown, Jr. Published (1980) by F. A. Davis, Philadelphia. Pp. 193; illustrated; indexed. Price $25.00.

This is the second volume of a series entitled *Contemporary Anesthesia Practice*. According to the editor, it "is not intended to be authoritative but simply suggests lines of management . . . (and) . . . consists of a pot-pourri of articles."

The book consists of 10 short chapters by different authors on various topics in the areas of hypertension, arrhythmias, and myocardial ischaemia and there is one chapter on congenital heart defects. The disadvantage of this approach is frequent repetition, for example, of factors affecting myocardial oxygen supply/demand relationships and the assessment of this balance using the V_5 lead of the e.c.g. However, every chapter is written in a readable style. Informality of approach is best illustrated by this excerpt: "contractility is difficult to define and can probably best be described as "oomph" ". Frequently evidence to support statements relies on personal experience and opinion and on occasion one would dispute sentiments expressed.

Despite these minor flaws, this is a very good collection of essays which can be warmly recommended to established anaesthetists.

Graham Smith

Malignant Hyperthermia. International Anesthesiology Clinics, Vol. 17, No. 4. Edited by B. A. Britt. Published (1979) by Little, Brown & Co., Boston. Price £16.55.

Malignant hyperpyrexia (MH, malignant hyperthermia) is an uncommon but important complication of anaesthesia which has achieved prominence in the past decade. Although there are now four books on this topic in hard-back, two of these have been reports of international symposia and have had a pronounced research slant. This book has been written for the practising anaesthetist and contains the relevant clinical information for diagnosing, treating and further investigating MH patients and their families. It is published as one of the volumes in the International Anesthesiology Clinics series.

Of the eight chapters only two are not directly relevant to the practising anaesthetist, namely a chapter on porcine MH and a second on the histopathology of MH muscle. Both these, however, add considerably to the overall interest of the book.

Most chapters are well referenced, though the first chapter on the acute crisis only has a further reading list and no direct textual references.

The last chapter concerns the treatment of the acute crisis. With the recent introduction of dantrolene into clinical practice, it is unfortunate that this drug has not been incorporated into the programme of treatment presented.

This book is a useful, simple and very readable account of complex conditions of which anaesthetists must be fully aware. I believe it would be suitable for inclusion in a hospital departmental library both for general interest and as a ready reference in time of crisis.

F. Richard Ellis

Clinical Pharmacology, 24th edn. Edited by R. H. Girdwood. Published by Baillière Tindall, London. Pp. 608; illustrated; indexed. Price £9.75.

It seems likely that any textbook which reaches a 24th edition has a high degree of reader acceptability. It is now almost 100 years old, but has been brought up to date constantly and still manages to cover the great majority of drugs used today. There are two general chapters, and that on the mechanisms of drug action could profitably be read by all clinicians, to combat our trial-and-error approach. One would, however, welcome a table setting out a wide range of drug interactions more clearly, in view of their practical importance.

The subject of adverse drug reactions is also well covered, including the medico-legal aspects of drug registration and the Committee on Safety of Medicines. Some guidance on the subject of drug trials would be of value, even to the undergraduate student, since he is unlikely to cover the subject elsewhere. Dependence on and misuse of drugs has a separate chapter which brings together the narcotics, ethanol and cannabis and clarifies one's ideas on the topic There is also a very full list of proprietary versus official names.

The value of a textbook of clinical pharmacology lies mainly in its completeness and this volume compares well with its larger rivals in practical terms For instance, the anaesthetist finding that a prospective patient is receiving emetine may wish to look up the possible side-effects of the drug. This and other substances used in specific infections are covered in detail, as well as all the currently available antibiotics. There is therefore no excuse for a casual antibiotic policy and sufficient information is given for planning a treatment regime in an intensive care unit or elsewhere. On the other hand, this is a textbook of pharmacology not therapeutics and, while the use of insulin in diabetes is discussed, its use in an intensive care unit for treating hyperkalaemia or stress hyperglycaemia is not mentioned.

The anaesthetist is unlikely to use a book of this kind for information on general anaesthetics, and the necessity for compression means that some information which an anaesthetist regards as important is omitted. For instance, the dangerous hypersensitivity reactions to propanidid and the pain on injection and muscle movements with etomidate are not mentioned. The hazards of administration of i.v. diazepam by the unskilled, and the fact that it is a general anaesthetic, are stressed. The authors might add, however, that because of its solvents, its i.v use is frequently accompanied by pain and eventually followed by venous thrombosis.

The book is therefore a valuable textbook of human pharmacology and covers all the drugs that the anaesthetist will meet clinically. The candidate preparing for the Primary Fellowship will still, however, need to know a little more of the application of these drugs in anaesthetic and intensive care medicine.

R. S. J. Clarke

OTHER BOOKS RECEIVED

Key Words in Anesthesiology, 2nd edn. By Nicholas M. Greene. Published by The Williams & Wilkins Company, Baltimore. Price: $8.25.

Printed in Great Britain by John Wright and Sons Ltd, at The Stonebridge Press, Bristol BS4 5NU

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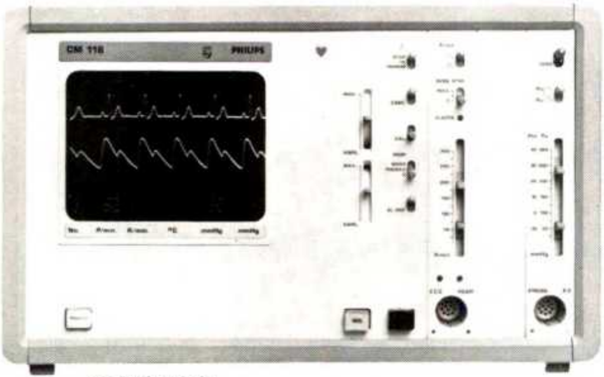

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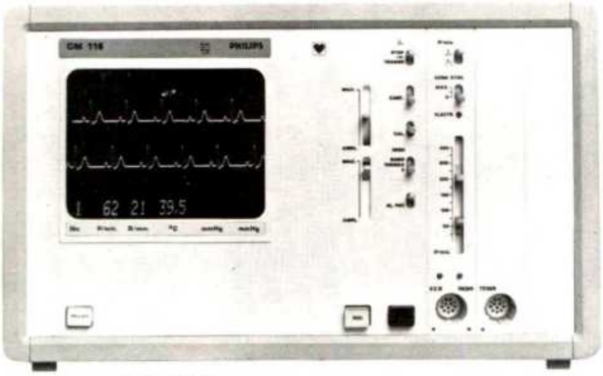

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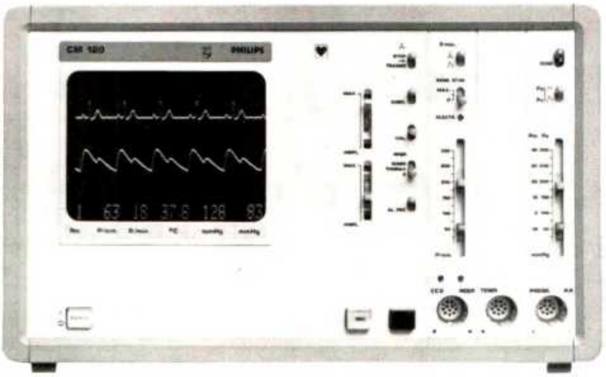

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 8 *Published monthly* AUGUST 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27.50, Airmail £50 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

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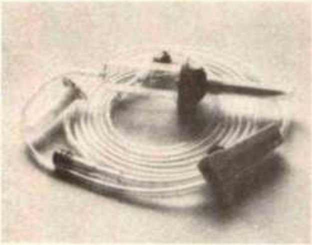

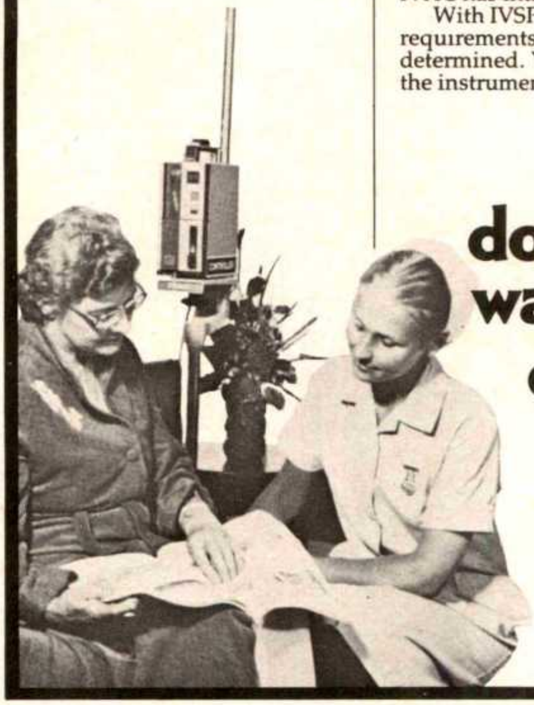

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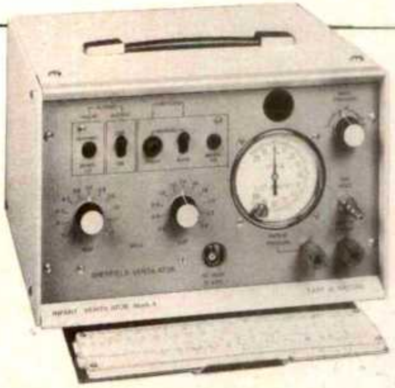

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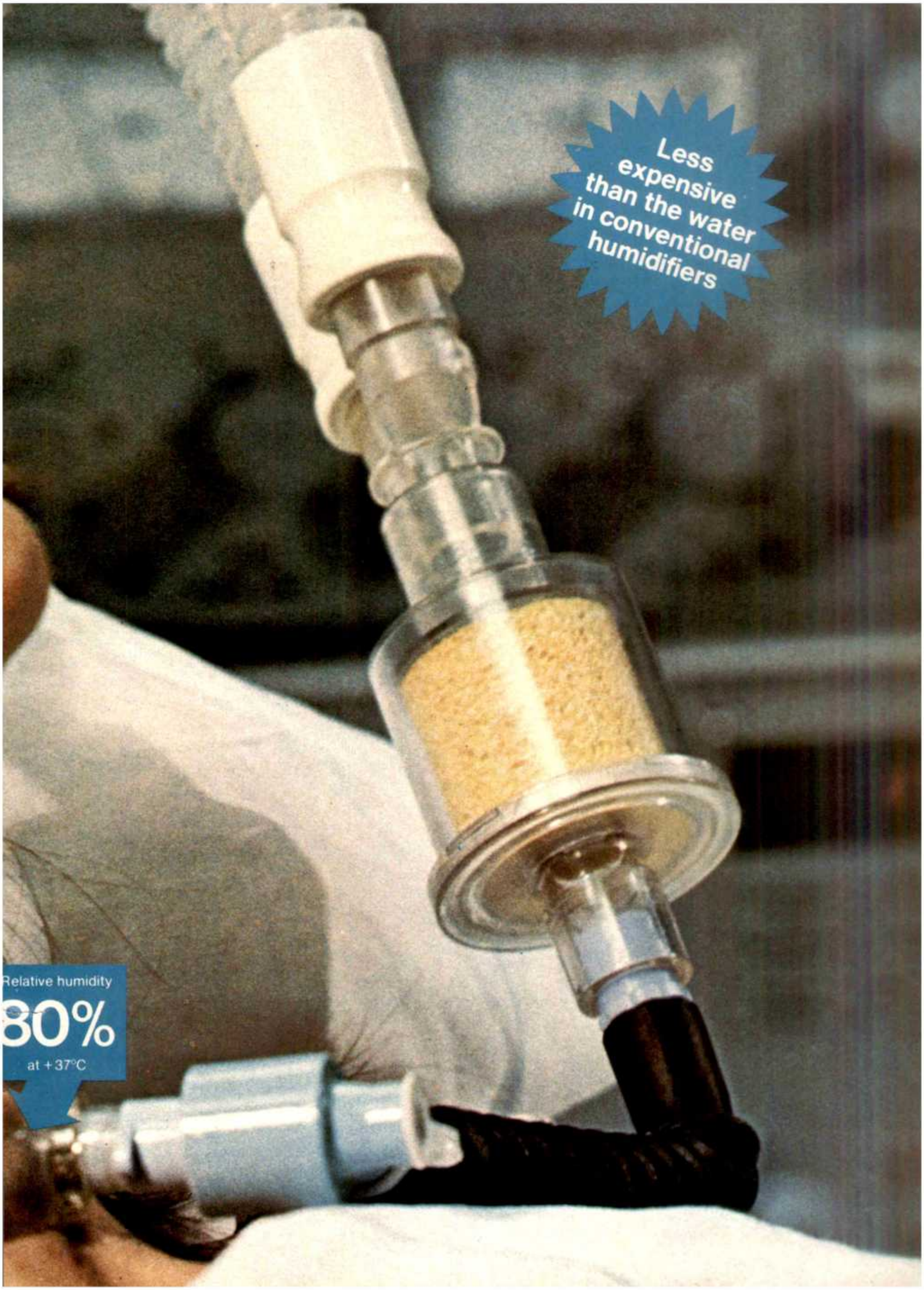
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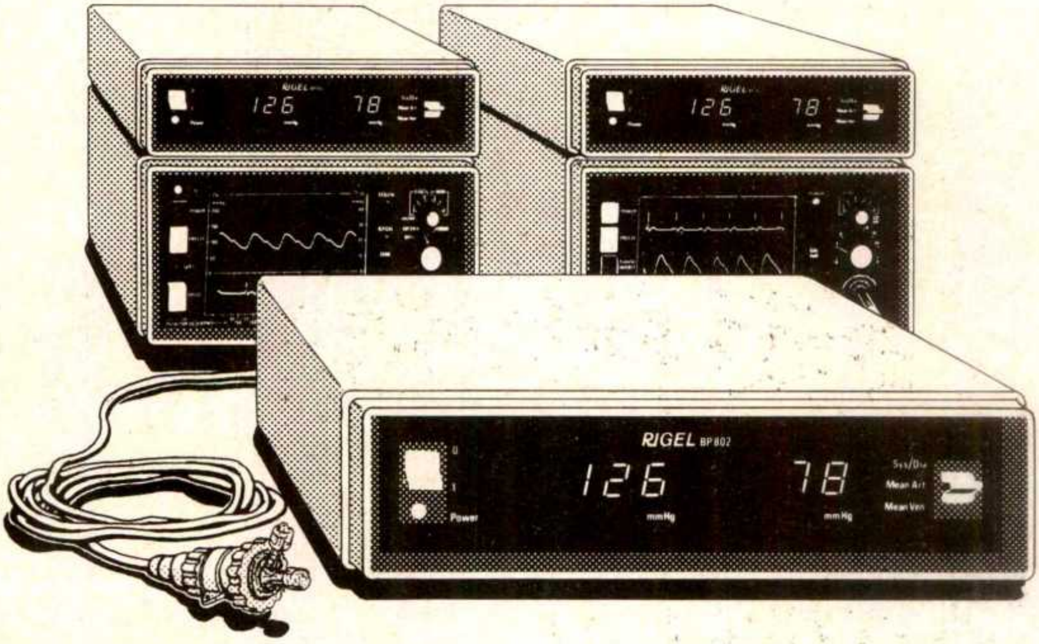

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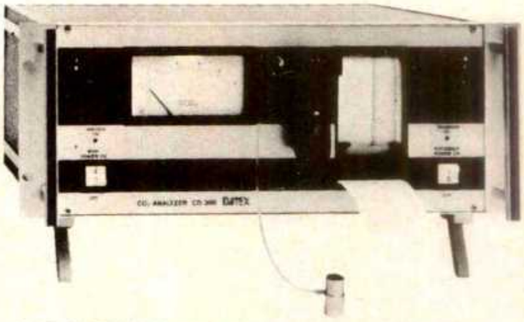

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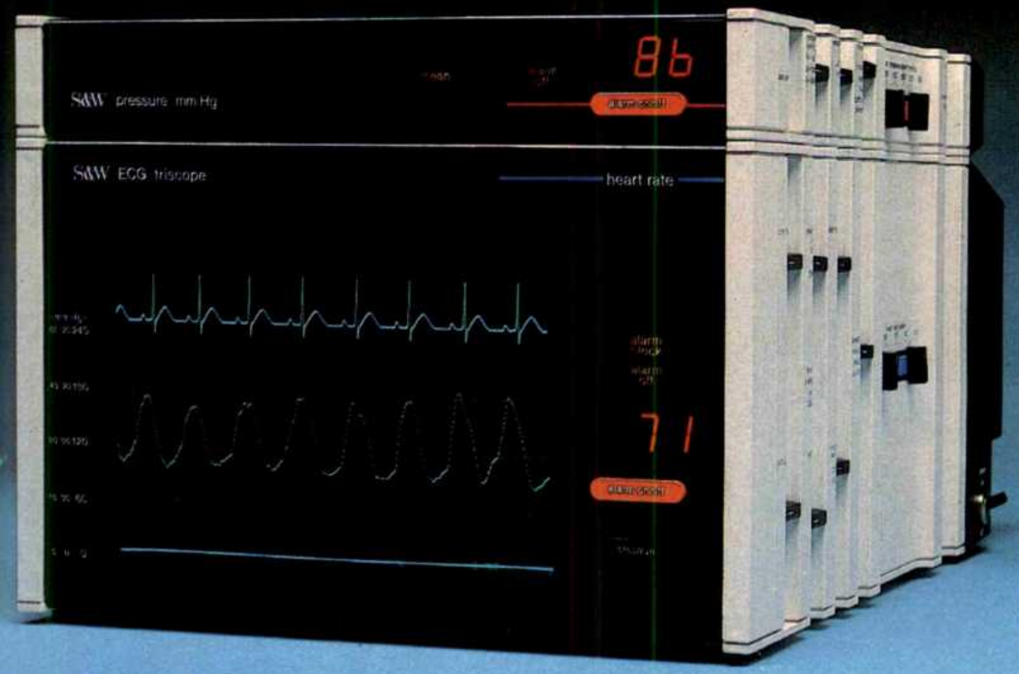

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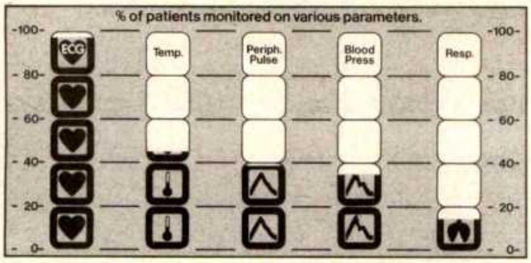

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ERRATUM

CONTROL OF THE EYE DURING GENERAL ANAESTHESIA FOR INTRAOCULAR SURGERY

Br. J. Anaesth., **52**, 673

The penultimate paragraph at the right side of p. 673 should read: "The increase in choroidal blood flow following i.v. acetazolamide has already been mentioned." (Not ...i.v. amiphenazole....)

Der Anaesthesist

The organ of the
Austrian, German and Swiss Societies
of Anaesthesiology and Reanimation

Edited by: A. Doenicke, München; R. Frey, Mainz; O. Mayrhofer, Wein; H. Schaer, Mennedorf
Managing Editor: A. Doenicke, München, Chirurgische Universitäts-Poliklivik, Anaesthesie, Pettenkoferstr. 8a, D-8000, München

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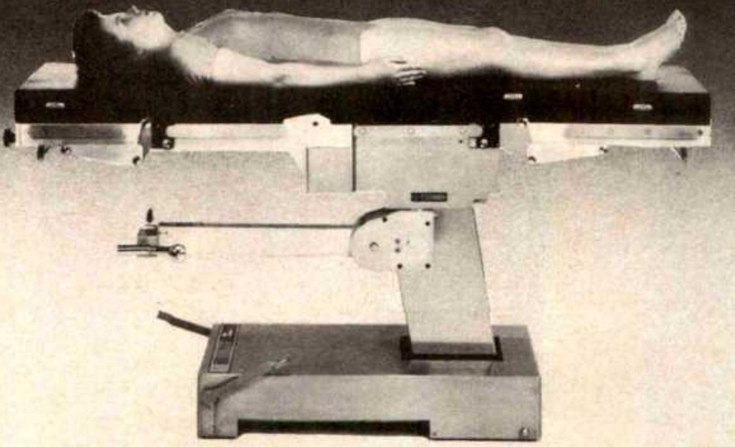

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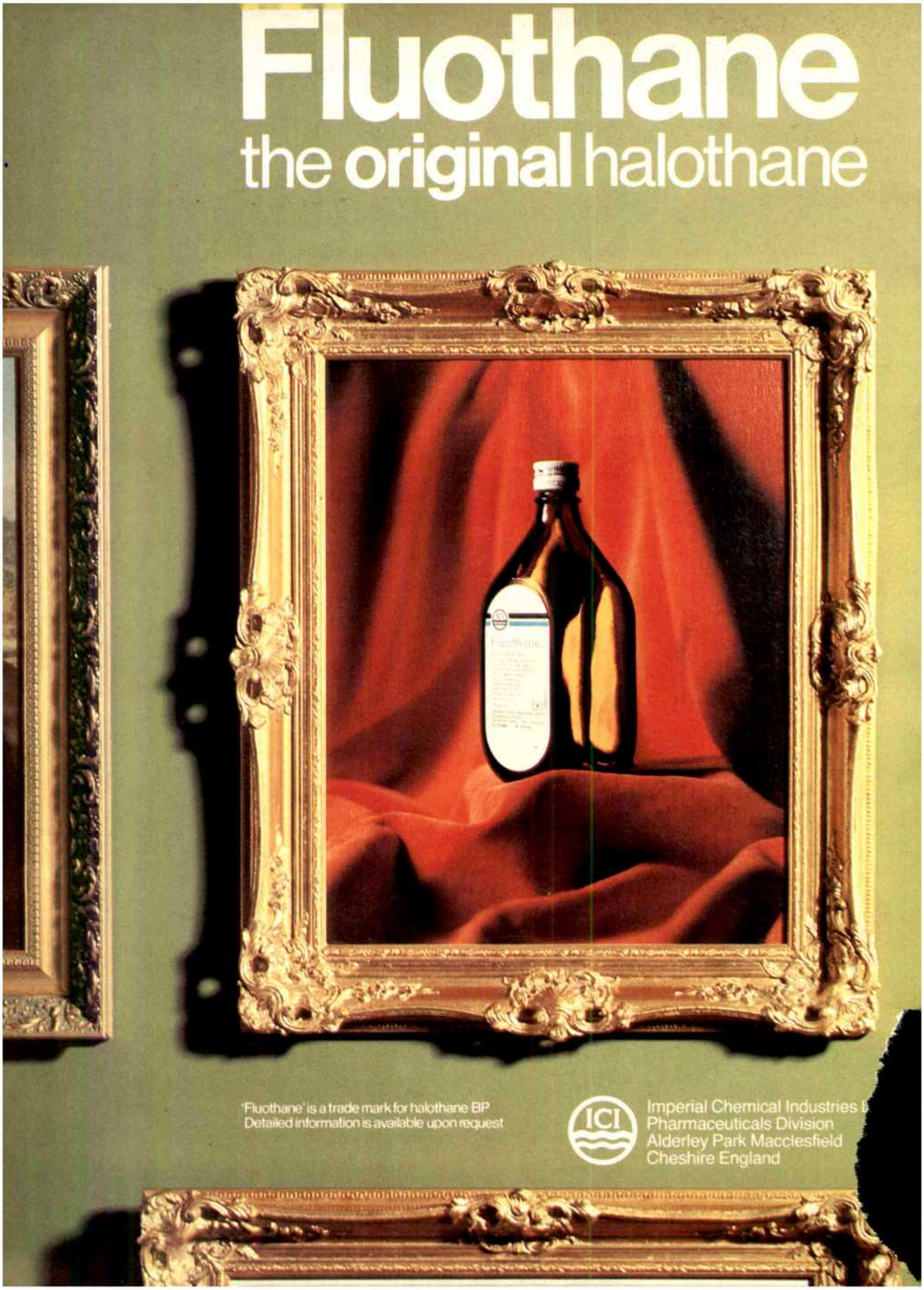

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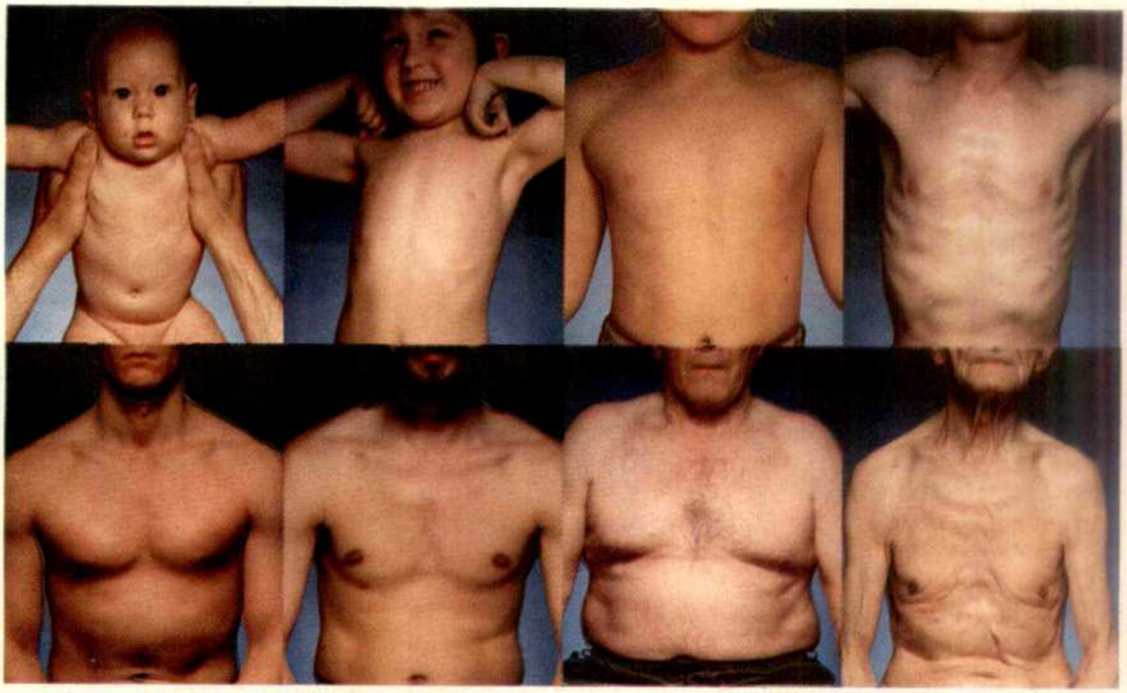

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EDITORIAL NOTE

As a footnote to the paper by Dixon and others (*Br. J. Anaesth.*, 1980, **52**, 525), reference was made to the British Medical Association and recommendations about the interval which should elapse after general anaesthesia before driving a motor vehicle. The 48-h recommendation referred to appears in Havard, J. D. J. (1968) *Medical Aspects of Fitness to Drive* (ed. A. Raffle), p. 50; London: Dorriston Ltd. Although Dr Havard is closely identified with the British Medical Association the statements made in his chapter do not constitute BMA policy. We regret any misunderstanding which may have arisen.

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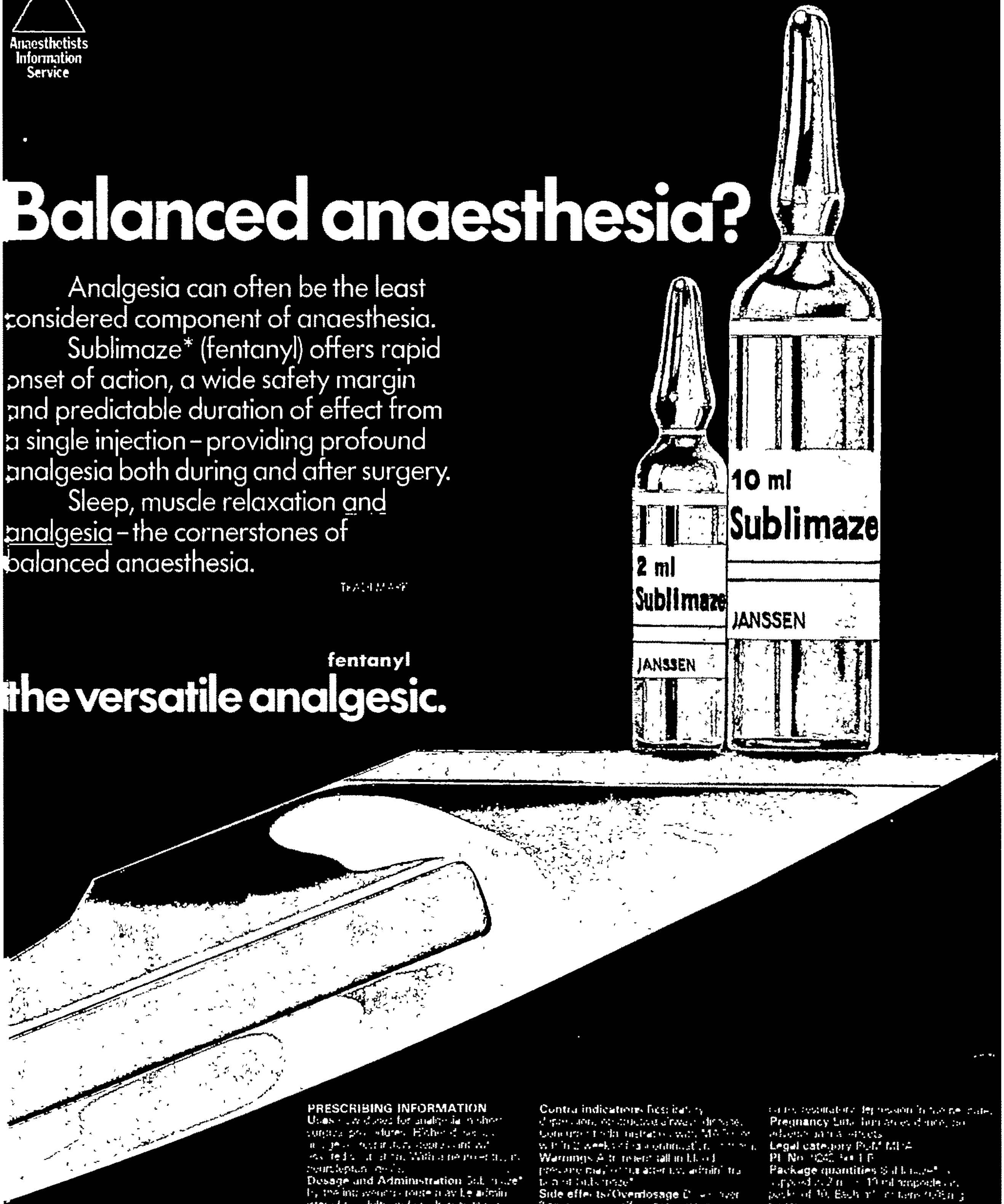

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 9 SEPTEMBER 1980

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EDITORIAL

DANTROLENE AND THE TREATMENT OF MALIGNANT HYPERTHERMIA

The availability in the United Kingdom in Autumn 1980 of a stable i.v. preparation of dantrolene for the treatment of malignant hyperthermia (MH) is an important milestone in the management of this rare, but often lethal, complication of anaesthesia. The development of a specific therapeutic agent for the clinical syndrome has followed from experimental studies on the porcine model, although there have been several "false starts," of which the most notable was procaine or procainamide.

Dantrolene, a hydantoin derivative, was synthesized by Snyder and colleagues (1967) and has been used orally to treat muscle spasticity (Dykes, 1975). It acts on skeletal muscle by interfering with the excitation–contraction coupling mechanism, so that the sarcolemmal action potential is no longer coupled or linked to the normal efflux of calcium ions within the muscle cell. Thus, there is a reduction in the availability of calcium ions for the contractile process (for review see Pinder et al., 1977). It is often claimed that the effects of dantrolene are specific for skeletal muscle, but recent studies have shown that dantrolene also depresses smooth muscle (Graves, Dretchen and Kruger, 1978), cardiac muscle (Meyer, Wesseling and Agoston, 1976) and catecholamine release from the adrenal medulla (Cohen and Gutman, 1979). It would be surprising if dantrolene had no effects on other calcium-coupled systems, although these are unlikely to be important at doses used to relieve muscle spasticity.

Harrison (1975) was the first to demonstrate the effectiveness of i.v. dantrolene in the treatment of MH in Landrace pigs. This observation was confirmed in Poland China pigs by Gronert, Milde and Theye (1976) and in Pietrain pigs by Hall, Lucke and Lister (1977) using dantrolene 7.5 mg kg^{-1}. In addition, Gronert, Milde and Theye (1976) showed that the i.v. administration of dantrolene 5 mg kg^{-1} afforded complete protection against porcine MH if given only 10 min before halothane and suxamethonium. Harrison (1977) found that oral dantrolene was also effective in preventing MH if given in two doses of 5 mg kg^{-1}, 24 and 4 h before anaesthesia. The data from the experiments on porcine MH are conclusive; dantrolene is effective both therapeutically and prophylactically.

The application of the results obtained in porcine MH to the clinical syndrome has been delayed by the difficulties in producing a stable i.v. preparation of dantrolene. However, a small pilot study has been undertaken with a suitable i.v. preparation at 45 hospitals in the United States and Canada. The criteria used for confirming the occurrence of MH in this study were very weak (for example, a tachycardia of 20 beat min^{-1} greater than baseline values, arterial $pH < 7.35$, $P_{CO_2} > 42$ mm Hg) and consequently many of the patients reported were undoubtedly not suffering from MH. Nevertheless there were three cases of MH in which the administration of dantrolene i.v., at doses ranging from 0.9 to 1.6 mg kg^{-1}, was associated with the rapid and complete resolution of the hyperthermic response. It seems likely that not only is dantrolene effective in the treatment of human MH, but also the dose required is considerably less than in the porcine syndrome.

The i.v. preparation of dantrolene will be available in vials containing sodium dantrolene 20 mg, mannitol 3 g and sodium hydroxide to produce a final pH of 9.5 on the addition of 60 ml of water. The use of alkaline mannitol as the solvent for dantrolene is a useful bonus as a diuresis is necessary during the treatment of MH to prevent the deleterious effects of myoglobin on renal tubular function. It is unfortunate that such a large volume of water is required to dissolve the contents of each vial because valuable time will be lost in preparing the solution. For example, administration of dantrolene 2 mg kg^{-1} to a 70-kg patient will need 420 ml of sterile water.

Oral dantrolene has been used recently as a prophylactic measure in a patient who was MH-susceptible (Pandit, Kothary and Cohen, 1979). Peak blood concentrations of dantrolene occur about 4 h after oral administration with a plasma half-life of 6–8 h (Herman, Meyer and Mecomber, 1972). Various regimes have been advocated for oral prophylaxis with dantrolene but it is my policy to confine pretreatment to the 24 h before surgery when the patient is given about 5 mg kg^{-1}. It is possible that a smaller dose of dantrolene may be equally effective, but it is essential to err on the side of caution until sufficient information is available on the use of oral dantrolene.

At present it is a difficult choice between the administration of prophylactic dantrolene for the MH-susceptible patient or reliance on the use of a "safe" anaesthetic technique. The effective prophylactic dose of dantrolene is similar to that at which adverse side-effects start to occur. A patient who is given oral dantrolene and suffers from any of the following symptoms: dizziness, blurred vision, incoordination, abdominal pain, diarrhoea, nausea and muscle weakness (Pandit, Kothary and Cohen, 1979; author's observations), may question the necessity of this life-saving therapy. Furthermore, the possible interactions of dantrolene with neuromuscular blocking drugs given during anaesthesia have yet to be thoroughly elucidated. A recent study by Flewellen, Nelson and Bee (1980) investigated the effects of dantrolene on neuromuscular blockade produced by tubocurarine. They found that neostigmine did not reverse the dantrolene-induced depression of muscle function and warn that this may contribute to respiratory inadequacy in the period after operation. On balance, the anaesthetist who is meeting the problem of anaesthesia for the MH-susceptible patient for the first time is advised to use oral dantrolene prophylactically. The anaesthetist with experience of such cases can probably rely on the avoidance of known triggering agents.

It is not the purpose of this editorial to describe in detail the treatment of MH (for which, see Ryan, 1977), but to indicate when and how i.v. dantrolene should be used. As soon as MH is diagnosed all potent inhalation anaesthetic agents must be discontinued, and the acidosis treated immediately by hyperventilation and the i.v. administration of sodium bicarbonate. Dantrolene is then injected in aliquots of 1 mg kg^{-1} at intervals of 5–10 min until MH is resolved, as shown by control of the acidosis, tachycardia, temperature and muscle tone. Dantrolene 2–3 mg kg^{-1} i.v. is probably sufficient to treat most cases of human MH, but up to 10 mg kg^{-1} has been used in the porcine syndrome without adverse side-effects (Gronert, Milde and Theye, 1976).

Some anaesthetists who have never seen a case of MH may question the need for purchasing an expensive drug, approximately £1 per mg, with a limited shelf-life of 18 months to 2 years. Dantrolene should be regarded, however, as cheap insurance against a possible anaesthetic death and be readily available in all hospitals in which anaesthetics are undertaken.

Anaesthetists in the United Kingdom who use i.v. dantrolene in MH will be asked to supply all clinical details to Eaton Laboratories, who market the drug, so that the data can be collected and analysed. This service is essential if the correct use of dantrolene is to be established and all anaesthetists are urged to co-operate, even if the diagnosis of MH is not subsequently confirmed.

Progress in the management of MH-susceptible patients has been painfully slow since the syndrome was first described 20 years ago. The use of dantrolene both orally and i.v. offers a unique opportunity to reduce the mortality rate significantly.

I am indebted to Eaton Laboratories, a Division of Morton–Norwhich Laboratories, for details of 19 patients treated with dantrolene in the Multicentre Study in North America.

G. M. Hall

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Br. J. Anaesth. (1980), **52**, 851

SOLUBILITY AND DISTRIBUTION OF HALOTHANE IN HUMAN BLOOD*

Y. C. PANG, P. E. REID AND D. E. BROOKS

SUMMARY

The interactions of halothane with five major constituents of human blood were studied by equilibrium dialysis. Haemoglobin, albumin, red cell membranes and triglycerides were found to contribute significantly to the solubility, and thus the transport, of halothane in whole blood. At physiological concentrations, γ-globulin had no detectable effect on the solubility of halothane. Absorption isotherms of halothane binding to haemoglobin and albumin suggest a possible positive co-operative effect, but complete saturation of the binding sites was not observed even when the aqueous phase was saturated with halothane. The number of halothane molecules bound per albumin molecule was not significantly affected by the presence of oleic acid. For red cell ghosts and triglyceride-rich micelles (chylomicrons and very low density lipoprotein), the adsorption isotherms suggested that halothane is solubilized within the hydrophobic regions. The distribution of halothane between cells and plasma calculated from the above equilibrium dialysis results was in reasonable agreement with the distribution in whole blood determined by an independent method.

Little is known about the mechanism of the transport of general anaesthetic agents in blood. Although there have been studies, on models, of the interaction of anaesthetics with both artificial membranes (Hill, 1974; Johnson and Bangham, 1969; Metcalfe and Burger, 1968; Trudell and Hubbell, 1976; Koehler, Fossel and Koehler, 1977) and haemoglobin and other proteins (Millar, Beard and Hulands, 1971; Laasberg and Hedley-Whyte, 1971; Schulman, Peisach and Wyluda, 1970; Hanisch et al., 1969; Barker et al., 1975) they do not provide quantitative information on the contribution of the various components of blood to the transport of anaesthetics. Since current theories of the action of anaesthetics favour an anaesthetic–lipid interaction (Eger, Saidman and Brandstater, 1965; Saidman et al., 1967; Schneider, 1968; Seeman et al., 1969; Seeman, Roth and Schneider, 1971; Halsey and Kent, 1972; Miller et al., 1972, 1973; Seeman, 1972, 1974; Halsey, 1974; Trudell, 1974; Ueda, Shieh and Eyring, 1974; Hansch et al., 1975; Richards, 1976; Haydon et al., 1977), one might expect that a significant proportion of the anaesthetic agent would be transported by the red cell membrane. However, there has been no conclusive evidence presented for or against this theory and it has been reported variously that the solubility of anaesthetics in blood has either a positive or a negative dependence on, or is independent of, haematocrit (Muehlbacher and Debon, 1966; Laasberg and Hedley-Whyte, 1970; Cowles, Borgstedt and Gillies, 1971; Eger, 1974; Ellis and Stoelting, 1975; Steward, Allot and Mapleson, 1975; Saraiva et al., 1977). These contradictory results are probably a result of the lack of both a systematic approach and precise knowledge of the composition of the systems examined. For example, in most investigations the concentrations of plasma proteins were not reported, although they are known (Chiou and Hsiao, 1974) to influence solubility.

To provide detailed information on this system, we have investigated the interaction of halothane (1,1,1-trifluoro-2-bromo-2-chloroethane), a representative, widely-used general anaesthetic, with haemoglobin, red cell ghosts, albumin (both fatty acid-free and in the presence of oleic acid), γ-globulin and triglyceride-rich micelles. The results obtained were used to calculate the distribution of halothane between cells and plasma and were compared with those obtained by a direct method.

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* This work was presented, in part, before the annual meeting of the Chemical Institute of Canada, June 1979. It was carried out by Y. C. Pang in partial fulfilment of the requirements for the degree of PH.D. of the University of British Columbia.

0007-0912/80/090851-12 $01.00

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MATERIALS AND METHODS

Materials

Silicone rubber septa, Reacti-vials (0.3 ml and 1.0 ml) and 25-ml screw-cap vials were obtained (Pierce Chemical Co., Rockford, Ill., U.S.A.) with gas-tight Teflon-lined seals and served as leak-proof containers for halothane. Such vials have been shown to be leak-proof for storage up to 2 weeks (Reid et al., 1978). Gas-tight syringes were obtained from the Hamilton Co., Reno, Nevada, U.S.A. Amicon CF50 and CF25 membrane ultrafilters were supplied by the Amicon Corp., Lexington, Mass. Halothane was obtained from Hoechst Pharmaceuticals, Montreal, Canada. All the reagents for triglyceride assay were obtained from Hycell Inc., Houston, Texas, U.S.A. 3,3′, 5,5′-Tetrabromo-m-cresolsulphonphthalein was obtained from American Monitor Corp., Indianapolis, Indiana, U.S.A. Human γ-globulin, fatty acid-free human albumin (less than 0.005% fat) and dialysis tubing were obtained from Sigma Chemical Co., St Louis, Mo. U.S.A. All other organic and inorganic chemicals used were of reagent grade from Fischer Scientific Co., Montreal, Canada.

Methods

Analytical methods. Haemoglobin concentration was assayed by the cyanohaemoglobin procedure (Van Kampen and Zijlstra, 1961), albumin by the method of Miyada and co-workers (1972) and triglyceride by the technique of Schmidt and Von Dahl (1968). Since anticoagulants may interfere with the triglyceride assay, sera used for the estimation of albumin and triglyceride were prepared from blood samples obtained with a plastic syringe without using an anticoagulant. The serum was produced by centrifugation in plastic Eppendorf centrifuge tubes at 10 000 *g* for 15 s. Red cells and red cell ghosts were counted in a Neubauer counting chamber (Dacie and Lewis, 1968) in the latter case using a phase-contrast microscope. Disodium EDTA (0.2% w/v) was used as the anticoagulant wherever necessary. The determination of halothane in aqueous solutions was performed by gas–liquid chromatography (GLC) as described previously (Reid et al., 1978).

Preparation of solutions. Phosphate buffered saline, pH 7.4, (PBS) was prepared from sodium phosphate 0.01 mol litre^{-1} buffer containing sodium chloride 150 mmol litre^{-1} and 0.02% (w/v) sodium azide.

Saturated solutions of halothane in saline were prepared by layering carefully 0.85% (w/v) sodium chloride solutions on to a bulk phase of halothane contained in Reacti-vials such that the two phases occupied an approximately equal volume. The vials were sealed by displacing excess saline in such a manner that no air bubbles were trapped in the vial and they were then equilibrated at either 4 °C or 37 °C without mixing. Equilibrium concentrations were determined by gas–liquid chromatography.

Haemoglobin. Red blood cells were obtained, from Red Cross blood, by centrifugation at 20 000 rev min^{-1} for 20 min in a Sorvall SS–34 rotor (max. 48 000 *g*). They were washed five times in four times their own volume of sodium chloride 150 mmol litre^{-1} and were haemolysed by the addition of an approximately equal volume of distilled water. The solution was centrifuged as above and the supernatant recovered. After five repetitions of the process the ghost-free solution was dialysed twice for 4 and 16 h respectively, against 10 volumes of PBS, and the haemoglobin solution was centrifuged as above. The final haemoglobin concentration used was 9.8 g dl^{-1}.

Albumin solution. Fatty acid-free albumin was dissolved in PBS either alone or with oleic acid, such that the final concentration of albumin was approximately 2.3 g dl^{-1} in each case. The oleic acid concentration used (approximately 14 mg dl^{-1}) is within the normal range of unesterified fatty acid in the plasma (Henry, Cannon and Winkelman, 1974).

γ-Globulin. Human γ-globulin dissolved in PBS at a final concentration of 0.7 g dl^{-1} was used for dialysis against halothane.

Triglyceride-rich micelles were prepared by a technical modification of the method of Hatch and Lees (1968). Blood (50 ml), taken from non-fasting healthy donors, was centrifuged at approximately 1000 *g* for 5 min and 4-ml aliquots of the plasma were loaded into six polyallomer tubes. Seven millilitre of a solution with a density of 1.006 g ml^{-1} (prepared by dissolving sodium chloride 11.40 g, disodium EDTA 0.1 g and 1 ml of sodium hydroxide 1 mol litre^{-1} in a total volume of 1.003 litre of water) was layered on the serum samples with a glass pipette by allowing it to run continuously but slowly down the side of the slightly inclined tubes. The pipette tip was maintained at about 1 cm above the level of the liquid in the tubes to avoid dripping and turbulence. The loaded tubes were centrifuged in a Beckman SW 41 rotor at 40 000 rev min^{-1} (min 120 000 *g*, max. 280 000 *g*) at 16–18 °C for 16 h and 1–3 ml of the white suspension of triglyceride-rich micelles (chylomicrons and very low density lipoprotein) was taken from the top of each tube, pooled, and dialysed successively, at 4 °C, against 1.0-litre portions of distilled water for 4 h and 16 h. A sample of the suspension was taken for triglyceride assay and to the remainder was added exactly 1/9 the volume of a 10X PBS buffer containing 1% (w/v) disodium EDTA.

Red cell ghost suspension. Ghosts were prepared from Red Cross blood and resealed by warming as described by Theodore and Kant (1974). The resealed ghosts were washed twice and resuspended in an approximately equal volume of PBS.

Dialysis of blood components against halothane. The apparatus used is shown in figure 1. A disc of cellulose dialysis membrane was placed carefully on top of a 0.3-ml Reacti-vial completely filled with a solution or a suspension of the blood component to be dialysed. The disc was sealed, finger tight, by means of the "O" ring (cut from a silicone rubber septum commercially available for these vials) fitted into the cap of the Reacti-vial. The vials were incubated for various time intervals at 37 °C with solutions of halothane in PBS contained in completely filled, sealed, 25-ml screw-cap vials; when red cell ghosts, γ-globulin and triglyceride micelles were being investigated the outer 25-ml vial was rotated slowly. On completion of the dialysis, duplicate samples were taken from the inner and outer vials for estimation of halothane concentration.

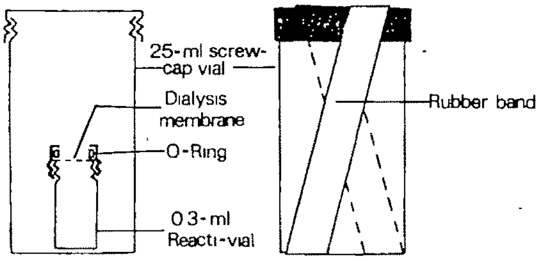

FIG. 1. Diagrammatic representation of the equilibrium dialysis assembly.

In those experiments in which the free halothane concentration was held constant and the triglyceride concentration varied, all the 0.3-ml Reacti-vials containing different concentrations of triglyceride were placed into one 500-ml reagent bottle. A gas-tight seal for this bottle was made by cutting a circular piece of Teflon (PTFE, Dupont) to fit the inside of the plastic screw cap. Otherwise the procedures were identical with the other dialysis experiments.

The number of halothane molecules bound per protein molecule was calculated using the formula:

$$\frac{\text{number of halothane molecules}}{\text{number of protein molecules}} = \frac{\dfrac{[\text{halothane}]\text{i}}{1-\bar{V}\,[\text{protein}]} - [\text{halothane}]\text{o}}{\dfrac{[\text{protein}]}{1-\bar{V}\,[\text{protein}]}} \times \frac{\text{mol. wt protein}}{\text{mol. wt halothane}} \qquad (1)$$

where [halothane]i = halothane concentration (g ml^{-1}) inside the 0.3-ml Reacti-vial; [halothane]o = halothane concentration (g ml^{-1}) outside the 0.3-ml Reacti-vial; [protein] = protein concentration (g ml^{-1}): $\bar{V}$ = partial specific volume of the protein.

For haemoglobin $\bar{V} = 0.749$ ml g^{-1}
mol. wt = 64 500 (Altman and Dittmer, 1972)

For albumin $\bar{V} = 0.733$ ml g^{-1}
mol. wt = 66 200 (Peters, 1975).

The number of halothane molecules per red cell ghost was calculated using the formula:

$$\frac{\text{number of halothane molecules}}{\text{number of red cell ghosts}} = \frac{\dfrac{[\text{halothane}]\text{i} - [\text{halothane}]\text{o}}{1-KC}}{\dfrac{C}{1-KC}} \times \frac{N_A}{\text{mol. wt halothane}} \qquad (2)$$

where C = number of ghosts per unit volume; K = volume of one ghost approximated by the product of the thickness and surface area of the ghost membrane, taken to be 2.4 nm (Fettiplace, Andrews and Haydon, 1971) and 136.9 μm^2 (Jay, 1975) respectively; N_A = Avogadro's number.

The number of grams of halothane per gram of triglyceride was calculated using the formula:

$$\frac{\text{wt. of halothane}}{\text{wt. of triglyceride}} = \frac{[\text{halothane}]\text{i} - [\text{halothane}]\text{o}}{[\text{triglyceride}]} \qquad (3)$$

Distribution of halothane between cells and plasma. A 10-ml gas-tight glass syringe fitted with a cap (made by removing the needle portion of a Luer Lok syringe needle and sealing the opening with solder) was weighed without the plunger and filled with approximately 10 ml of blood (anti-coagulated with EDTA) from a non-fasting healthy donor and reweighed. An accurately known volume (less than 1 ml) of a normal saline solution saturated with halothane at room temperature was added, to give a final halothane concentration of approximately 40 20 or 5 mg dl^{-1} respectively and the plunger was inserted immediately with the needle end of the syringe downward. The syringe was inverted, the cap removed, and the plunger pressed to expel as much air as possible without losing any significant amount of blood. The syringe was resealed with the cap and rotated, end to end, very slowly for 30 min. Six 1-ml Reacti-vials were filled with blood from this syringe and were equilibrated by very slow rotation at 37 °C. At the end of the equilibration, four of the vials were centrifuged in a Sorvall HB-4 rotor at 4500 rev min^{-1} (max. 2870 g) for 15 min, which was sufficient to sediment almost all the platelets (Schauberge, Kambayashi and Makagawa, 1976). Plasma samples were then taken for analysis of halothane concentration. Blood samples from the same set were analysed also for halothane concentration before and after the equilibration.

Blood samples with artificially decreased and increased triglyceride concentrations were prepared by separating cells and plasma then centrifuging the latter in a Beckman SW 41 rotor at 41 000 rev min^{-1} (min 130 000 g, max 290 000 g) for 4 h. The first and the last of the 11 ml in each centrifuge tube was discarded, and the remaining plasma was reconstituted with cells to the original haematocrit. This *triglyceride-poor blood sample* was divided into two 10-ml portions. To one of these was added approximately 0.4 ml of a highly concentrated triglyceride preparation (previously obtained by concentrating the triglyceride-rich micelle fraction from 25 ml of plasma to 0.5 ml using an Amicon CF50 membrane ultrafiltrater) to yield a *triglyceride rich blood sample.* Aliquots (1 ml) were removed from each sample for the assay of triglyceride and the remainder was used in dialysis experiments. Before the triglyceride assay the plasma samples were washed throughly with saline on an Amicon CF-25 membrane ultrafilter to remove EDTA.

The distribution of halothane between cells and plasma was calculated from the equations:

$$[\text{halothane}]\text{b} = \frac{\text{Hc}}{100}[\text{halothane}]\text{c} + (1 - \frac{\text{Hc})}{100}[\text{halothane}]\text{p} \qquad (4)$$

Percent of halothane in plasma

$$= \frac{(100 - \text{Hc})\,[\text{halothane}]\text{p}}{[\text{halothane}]\text{b}} \qquad (5)$$

$$\text{Percent of halothane in cells} = \frac{\text{Hc}\,[\text{halothane}]\text{c}}{[\text{halothane}]\text{b}} \qquad (6)$$

where [halothane]b = experimentally determined halothane concentration (mg dl^{-1}) in blood; [halothane]p = experimentally determined halothane concentration (mg dl^{-1}) in plasma; [halothane]c = halothane concentration in cells; Hc = 100 × volume fraction occupied by cells.

RESULTS

Preliminary experiments were performed in order to determine the time required to achieve equilibrium under the conditions employed in both the equilibrium dialysis studies and the investigations of halothane distribution between the cells and plasma of whole human blood. Equilibration times were found by dialysing samples with approximately the same halothane concentration and analysis for halothane concentration within and without the 0.3-ml Reacti-vials until the halothane concentrations became constant within the experimental error. The following equilibration times were established: haemoglobin, 92 h; albumin, 96 h; red cell ghosts, 44 h; triglyceride, 47 h; distribution between cells and plasma, 20 h.

Figures 2 and 3 show the results of dialysis experiments with haemoglobin and albumin respectively; each data point on these cure represents one independent dialysis experiment. As seen in figure 2, the average number of halothane molecules bound to each haemoglobin molecule increased from 0 to approximately 5 as the free halothane concentration increased to saturation. The slope of the curve decreased

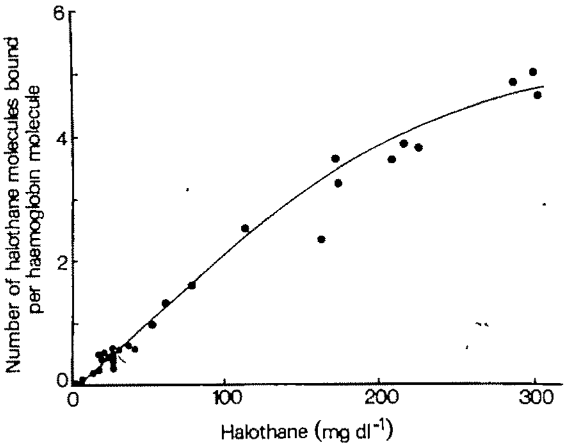

FIG. 2. Adsorption of halothane to haemoglobin at 37 °C.

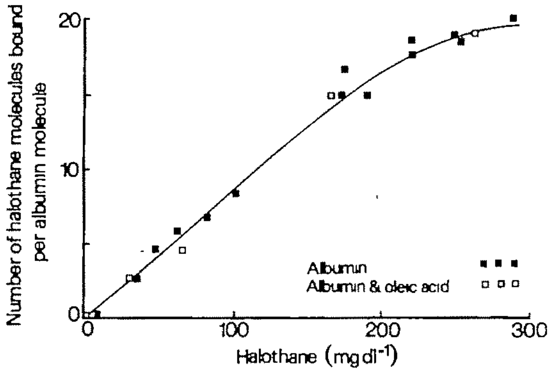

FIG. 3. Adsorption of halothane to albumin at 37 °C.

gradually with increasing free halothane concentration, but it did not level off to a plateau when the saturation concentration of halothane was reached. The curve obtained with albumin (fig. 3) was qualitatively similar to that for haemoglobin except that the average number of halothane molecules bound to each albumin molecule was much greater, reaching approximately 20 when the buffer was saturated with halothane. The adsorption of halothane to albumin containing bound oleic acid was indistinguishable from that of the anaesthetic to fatty acid-free albumin (fig. 3).

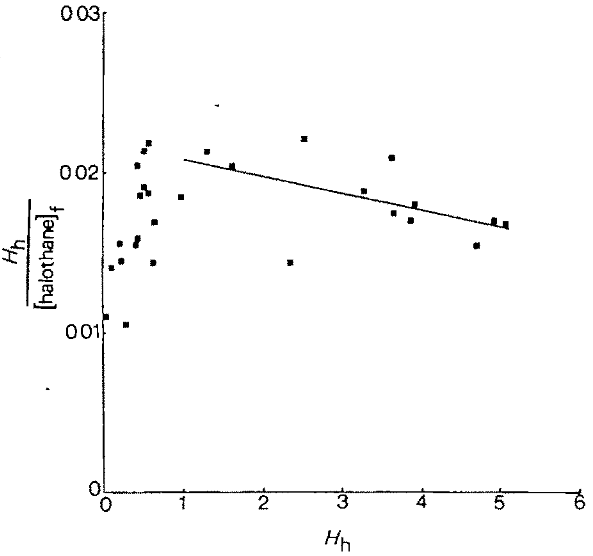

FIG. 4. Scatchard Plot of halothane binding to haemoglobin at 37 °C. H_h = number of halothane molecules bound per haemoglobin molecule; [halothane]$_f$ = free halothane concentration in solution.

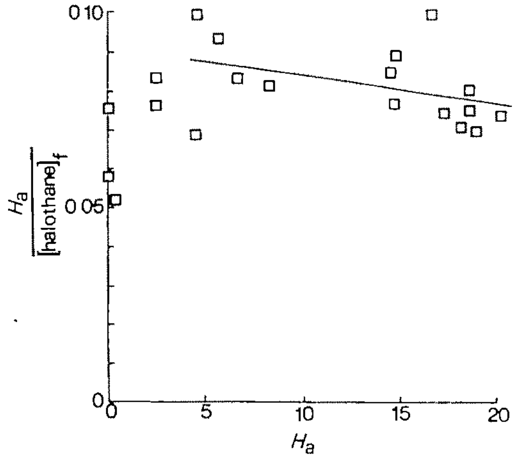

FIG. 5. Scatchard Plot of halothane binding to albumin at 37 °C. H_a = number of halothane molecules bound per albumin molecule; [halothane]$_f$ = free halothane concentration in solution.

The results were analysed also by the Scatchard method (Marshall, 1978), as shown in figures 4 and 5. Using the Scatchard equation, linear regression of those results obtained from equilibrium dialysis when the number of halothane molecules bound per haemoglobin molecule was larger than 1 and when the number of halothane molecules bound per albumin molecule was larger than 4 gave a total number of 20 ± 6 (95% confidence limit) and 130 ± 29 (95% confidence limit) sites for halothane on each haemoglobin and albumin molecule, respectively.

No binding to γ-globulin could be detected at the protein concentration used over a range of halothane concentration of 10 to approximately 100 mg dl^{-1}.

In contrast to the results obtained with haemoglobin and albumin, the slopes of the adsorption isotherms for red cell ghosts (fig. 6) and triglyceride-rich micelles (fig. 7) increased with increasing halothane concentrations, up to saturation of the aqueous phase, the change in slope being more pronounced with the triglyceride-rich micelles. The results shown in figure 7 were obtained at a constant triglyceride concentration of 83 mg dl^{-1}. As shown in figure 8, when the free halothane concentration was kept constant at 9.2 mg dl^{-1}, there was a linear relationship between the quantity of halothane solubilized and triglyceride concentration.

Table I compares the experimentally determined distribution of halothane between the cells and plasma for three normal blood samples at different halothane concentrations; and for two samples, from the same donor, with different triglyceride concentrations with the theoretical distribution calculated from figures 2, 3, 6 and 7 using the values determined experimentally for the cell count and the concentrations of albumin, haemoglobin and triglyceride. Calculations using figures 2, 3, 6 and 7 were performed using the linear regression equation determined from those data with free halothane concentrations of less than 150 mg dl^{-1}. Table II shows the theoretical distribution calculated from the "normal" physiological values (Henry, Cannon and Winkelman 1974) for the components under study.

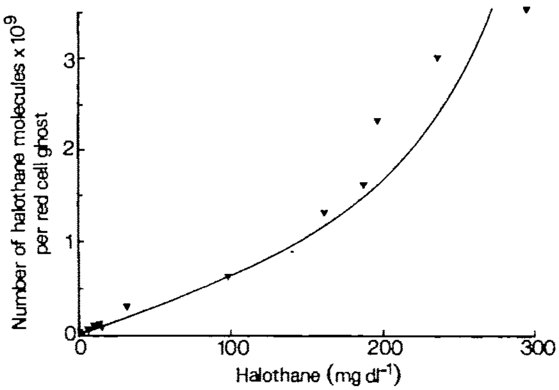

FIG. 6. Absorption of halothane to red cell ghosts at 37 °C.

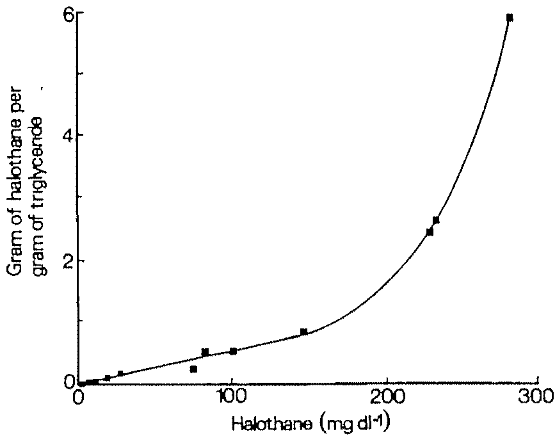

FIG. 7. Absorption of halothane to triglyceride-rich micelles at a constant triglyceride concentration of 83 mg dl^{-1} at 37 °C.

TABLE I. *Distribution of halothane between cells and plasma. Results obtained from five different blood samples*

Plasma triglyceride (mg dl^{-1})	[halothane] (mg dl^{-1}) in whole blood		% Halothane			
			Calculated from composition and dialysis results		From measurement in whole blood and plasma	
	Before equilibration	After equilibration	Plasma	Cell	Plasma	Cell
	42.8	41.7	38	62	48	52
	23.9	23.4	37	63	49	51
	3.8	4.2	38	62	49	51
33		25.1	28	72	39	61
183		25.7	34	66	48	52

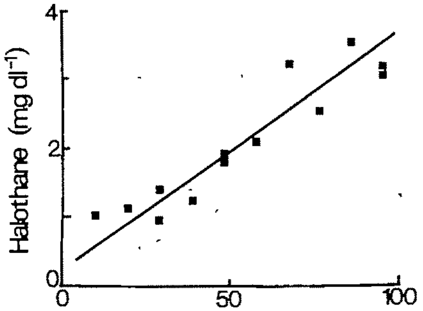

FIG. 8. Absorption of halothane to triglyceride-rich micelles at a constant free halothane concentration of 9.2 mg dl^{-1} at 37 °C.

TABLE II. *Distribution of halothane in blood calculated from the results of equilibrium dialysis. Hc assumed to be 45*

Blood component	Contribution to halothane solubility (% of total)
Plasma	
Albumin (4.3 g/dl of plasma)	16
Triglyceride (100 mg/dl of plasma)	6
Water	15 (free halothane)
Cells	
Red cell membrane (4.5×10^9 RBC/ml of blood)	40
Haemoglobin (14.5 g/dl of blood)	13
Water	10 (free halothane)

The linear regression equations used were:

$$H_h = 0.0223\ [\text{halothane}]_f - 0.119 \quad (7)$$
$$H_a = 0.0830\ [\text{halothane}]_f - 0.0294 \quad (8)$$
$$H_g = 6.28 \times 10^6\ [\text{halothane}]_f + 3.15 \times 10^7 \quad (9)$$
$$H_t = 0.00537\ [\text{halothane}]_f - 0.0170 \quad (10)$$

where $[\text{halothane}]_f$ = free halothane concentration in mg dl^{-1}; H_h = number of halothane molecules bound per haemoglobin molecule; H_a = number of halothane molecules bound per albumin molecule; H_g = number of halothane molecules solubilized per red cell ghost; H_t = gram of halothane solubilized per gram of triglyceride.

DISCUSSION

The shape of the adsorption isotherms of halothane to haemoglobin and albumin suggests that halothane is stabilized on a finite number of sites on the protein surface. Since halothane is very soluble in oil and quite insoluble in water (Steward et al., 1973), these are presumably hydrophobic sites, the bound halothane molecules being stabilized by hydrophobic interactions. As the isotherms do not level off to a plateau, the hydrophobic sites were not saturated even when the aqueous phase was saturated with halothane. Presumably the decrease in free energy associated with the interaction of hydrophobic molecules with the protein is less favourable than that accompanying self-association between the hydrophobic molecules when the solution is saturated (Tanford, 1973).

Although the adsorption isotherms for haemoglobin and albumin were qualitatively similar, at any given halothane concentrations many more halothane molecules were bound to albumin. This is to be expected as albumin is considered generally to be a carrier protein for small hydrophobic molecules (Peters, 1975) such as the plasma fatty acids. Since it has been estimated that less than 0.01% of the total unesterified fatty acid is free in the plasma (Goodman, 1958) and that 33% of the fatty acid bound to albumin is oleic acid (cis-9-octadecenoic acid; Saifer and Goldman, 1961) it was desirable to investigate the effect of oleic acid upon the binding of halothane to albumin. Figure 3 shows that oleic acid, at physiological concentrations, had no significant effect on the binding of halothane to albumin. This result is open to several interpretations. (i) Halothane and oleic acid do not compete for the same sites. This seems unlikely because both would be expected to bind to hydrophobic sites, although halothane and oleic acid, being quite different in molecular dimensions, may bind preferentially to different sites. (ii) The number of sites is large enough that the binding of oleic acid does not significantly reduce the number of sites available for halothane. (iii) The binding of oleic acid to albumin creates new hydrophobic sites for halothane. The last two interpretations are not mutually exclusive, but we do not have enough evidence to distinguish between them at present.

Figures 4 and 5 show the equilibrium results expressed graphically according to the Scatchard equation, which assumes that there is a finite number of identical but independent sites on a protein molecule for interaction with halothane. If this assumption is valid, the resulting graph should show a straight line with a negative slope. This is obviously not true in the case of binding of halothane to albumin and haemoglobin. Figures 4 and 5 both appear to have an initial positive slope followed by a less pronounced negative slope. Thus binding to identical and independent sites does not occur. The initial positive slope suggests a positive co-operative effect. The dimension of the surface sites has been suggested as a possible explanation of such co-operative effects (Tanford, 1973). If a site is large enough to accommodate more than one small molecule, it could be energetically more favourable for a second small molecule to bind to the same site after the first is already bound. When the initial positive slopes are ignored, linear regression of the data points with negative slope give a total number of sites on haemoglobin and albumin of 20 ± 6 and 130 ± 29 respectively for the binding of halothane.

The shape of the adsorption isotherm of halothane to red cell ghosts suggests that the nature of the interaction between halothane and the red cell membrane and that between halothane and haemoglobin or albumin are very different. Since halothane is hydrophobic and not surface active, it could presumably be "solubilized" within the hydrophobic region of the membrane. Thus the "bound" halothane would not be localized to fixed sites within the fluid membrane. The data suggest that it is more favourable for halothane to move into a membrane which has already incorporated some halothane molecules. Possibly the halothane molecules initially accommodated within the membrane distort it and lead to a less organized structure, which is more capable of accommodating more anaesthetic. In a study of the effect of n-alkanes on black lipid bilayer membranes (Haydon et al., 1977), it was found that an increase of alkane concentration caused an increase in the hydrophobic thickness of the black lipid bilayer as calculated from electrical capacity of the bilayer. The slope of the thickness–concentration curve increased with increasing alkane concentration in a way similar to that found for the halothane-ghost system. Our results are therefore qualitatively similar to those of Haydon and colleagues (1977).

Considerable evidence has been accumulated to indicate that the site of action of anaesthetics is at the cell membrane. The data presented here show directly that a significant amount of a general anaesthetic is capable of being bound by these structures.

In plasma, triglyceride is transported as protein-lipid micelles, predominantly in chylomicrons and very low density lipoproteins (VLDL) which consist of 88% and 56% triglyceride respectively (Osborne and Brewer, 1977). The adsorption isotherm of halothane binding to these triglyceride-rich micelles qualitatively resembles that for the red cell membrane, consistent with the fact that membranes and micelles share a somewhat similar architecture, that is, a hydrophobic core surrounded by a hydrophilic surface.

When dogs were anaesthetized with 1–2.5% inspired halothane, the steady state arterial halothane concentration was in the range of 10–30 mg dl^{-1} (Pang et al., in preparation). For humans, the results were similar except that the arterial halothane concentration was generally less than that for dogs at the same inspired concentration (Pang, Reid and Brooks, unpublished data), although we do not have extensive data. Thus the range of halothane concentration of clinical interest lies entirely within the linear region of figures 2, 3, 6 and 7, and the calculation obtained from equations (7)–(10) should be applicable under normal clinical conditions.

It is apparent that all the major components of human blood tested except γ-globulin (albumin, triglyceride, haemoglobin and red cell membranes) contribute significantly to the solubility, and hence the transport of halothane in blood. Using these results in combination with the saline/gas partition coefficient (taking an average value of 0.74 (Steward et al., 1973)), the blood/gas partition coefficient was calculated to be 2.6. This is in reasonable agreement with the experimentally determined value of 2.4 (Steward et al., 1973). Our data indicates, therefore, that the solubility of halothane in blood will increase with increases in albumin, triglyceride, haemoglobin and haematocrit, either singly or in combinations. Experimental observations on these relationships are, however, in conflict. Several investigators (Hans and Helrich, 1966; Lowe and Hagler, 1969; Cowles, Borgstedt and Gillies, 1971) have reported a decrease in solubility with an increase in haematocrit, while other studies have shown that the solubility of halothane is independent of the haematocrit (Saraiva et al., 1977), that halothane is less soluble in blood of low haematocrit (Ellis and Stoelting, 1975) or more soluble in blood of high haematocrit (Steward, Allot and Mapleson, 1975). It has also been reported that lipid concentration either increased (Larson, Eger and Severinghaus, 1962; Wagner, Naumann and Laravuso, 1974; Saraiva et al., 1977) or was not correlated with (Munson et al., 1978) the solubility of halothane, and that the solubility was dependent upon the albumin : globulin ratio (Laasberg and Hedley-Whyte, 1970). Saraiva and colleagues (1977) studied the effects of the concentrations of haemoglobin, serum albumin, globulin, total protein, triglyceride and cholesterol, the haematocrit, and the albumin : globulin and albumin : total protein ratios upon the solubility of halothane in blood and were able to demonstrate a statistically significant correlation only with serum triglyceride. Munson and co-workers (1978) were, however, unable to demonstrate this correlation, possibly because they used a narrower range of triglyceride concentrations and a smaller number of samples.

In the studies referred to above, the effect of various blood components upon the solubility of halothane was inferred indirectly from changes in the partition coefficient, defined as the ratio at equilibrium of the halothane concentration in the blood phase to that in the gas phase. Such changes are slight even when the concentration of a contributing blood component changes drastically, as exemplified by the two apparently conflicting reports (Saraiva et al., 1977; Munson et al., 1978) on the effect of changing the triglyceride concentration. Thus, if the normal concentration range of a particular blood component is small, as is generally the case, the change in the partition coefficient may be too small to be detected. Furthermore, when whole blood samples are used, the effect of random changes in the concentration of all the blood components can mask the effect of changes in the concentration of a particular component, hence decreasing the chance of finding a statistically significant correlation. In other words, the lack of a statistically significant correlation between the partition coefficient and the concentration of a certain blood component does not necessarily imply that the blood component does not contribute to the solubility of halothane, it may mean simply that the analytical method used is not sensitive enough to detect the contribution of the various blood components. It is not surprising, therefore, that the only statistically significant correlation found by Saraiva and colleagues (1977) was that for triglycerides, since triglyceride had the widest normal range in the blood samples used in that study. Further, as seen in table I, a large increase in plasma triglyceride concentration resulted in a detectable change in distribution of halothane in favour of the plasma in the present work.

The distribution of halothane between cells and plasma calculated from the equilibrium dialysis studies agrees reasonably well with that from the direct measurements on whole blood. There is a systematic difference, however, between the distributions determined by the two methods, the proportion of halothane found by the direct assay of the plasma being consistently greater than that calculated from the results of the dialysis method. This discrepancy can be accounted for, at least partially, by binding of halothane to those plasma proteins which were not investigated by equilibrium dialysis. Because of the small total membrane area associated with leukocytes and platelets, their contribution can be neglected. Plasma proteins other than albumin and γ-globulin constitute approximately 30% of the total plasma proteins (Henry, Cannon and Winkelman, 1974). If it is assumed that equal weights of albumin and of plasma proteins other than albumin and γ-globulin bind the same amount of halothane, then the discrepancies between the two estimates of distribution disappear. This assumption is unlikely to be valid, however, since the unaccounted-for plasma proteins probably have a smaller binding capacity for halothane than has albumin.

Also, lipids present in lipoproteins other than chylomicrons and VLDL (LDL, HDL and VHDL) have not been investigated. However, it is difficult to assess the importance of all the lipoproteins because the relative amounts of triglyceride, cholesterol and phospholipid are different for each lipoprotein; and the relative amounts of the lipoproteins are dependent upon the state of the individual when the blood sample was taken. However, it is reasonable that cholesterol and phospholipid also contribute to the solubility of halothane in plasma and thus could conceivably account for the discrepancy.

The concentration of haemoglobin also may account for the observed results. The haemoglobin concentration used in the dialysis experiments was approximately 2/3 that of the normal haemoglobin concentration of whole blood, or less than 1/3 of the actual haemoglobin concentrations within the red cells. Since haemoglobin molecules are concentrated within the volume of the intact red cells, intermolecular interaction could reduce the amount of halothane bound per molecule (Laasberg and Hedley-Whyte, 1970). In this situation the equilibrium dialysis results for the adsorption of halothane to haemoglobin would be an overestimate of the actual adsorption occurring in whole blood. Consequently an overestimate would be made of the distribution of halothane between cells and plasma in favour of the cell fraction.

A further consideration is that the same regression equations were used in the calculations for all the blood samples. Therefore any random error in the estimation of halothane bound to a particular blood component will be converted to a systematic error.

The claims that the solubility of halothane in blood has a negative dependence on haematocrit (Hans and Helrich, 1966; Lowe and Hagler, 1969; Cowles, Borgstedt and Gillies, 1971) are difficult to evaluate, because complete data regarding the time required to reach equilibrium were not given. However, in the study of Laasberg and Hedley-Whyte (1970) in which it was shown that equilibrium was established, the value of the partition coefficient obtained for blood was greater than that for plasma, which indicated, in agreement with our study, that the proportion of halothane in the cells is slightly greater than that in the plasma.

ACKNOWLEDGEMENTS

This work was supported by a grant from the British Columbia Heart Foundation. One of us (Y.C.P.) wishes to thank the University of British Columbia for the award of a University Summer Research Scholarship and a University Graduate Fellowship. We are grateful to Dr George Gray for the haemoglobin analyses performed at the Hematology Laboratory of Vancouver General Hospital.

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SOLUBILITE ET REPARTITION DE L'HALOTHANE DANS LE SANG

RESUME

L'interaction de l'halothane avec cinq importants constituants du sang humain a été étudiée par dialyse d'équilibrage. On a trouvé que l'hémoglobine, l'albumine, les membranes des hématies et les triglycérides contribuent de façon significative à la solubilité, et donc au transport, de l'halothane dans le sang complet Aux concentrations physiologiques, la globuline γ n'a pas eu d'effet décelable sur la solubilité de l'halothane. Les isothermes d'absorption de l'halothane se liant à l'hémoglobine et à l'albumine semblent indiquer qu'il y a un effet coopératif positif, mais on n'a pas remarqué de saturation totale des sites de liaison même lorsque la phase aqueuse a été saturée d'halothane. Le nombre des molécules d'halothane liées par molécule d'albumine n'a pas été significativement affecté par la présence d'acide oléique. Dans le cas des stromas et des micelles riches en triglycérides (hémoconies et lipoprotéines à très faible densité) les isothermes d'adsorption semblent indiquer que l'halothane est solubilisé au sein des zones hydrophobes. La répartition de l'halothane entre les cellules et le plasma, qui a été calculée à partir des résultats obtenus avec la dialyse d'équilibrage mentionnée plus haut, s'accorde raisonnablement avec la répartition dans le sang entier établie par une méthode independante

LOSLICHKEIT UND VERTEILUNG VON HALOTHAN IM BLUT

ZUSAMMENFASSUNG

Die Wechselwirkungen zwischen Halothan und fünf Hauptbestandteilen des menschlichen Blutes wurden mittels Gleichgewichts-Dialyse studiert. Hamoglobin, Albumin, Rotzellenmembranen und Triglyzeride trugen wesentlich zur Löslichkeit bei, und damit auch zur Transportierung von Halothan im Vollblut bei. Bei physiologischen Konzentrationen hatte Gammaglobulin keinen erkennbaren Effekt auf die Loslichkeit von halothan. Absorptions-Isothermen der Halothanbindung an Hamoglobin und an Albumin lassen einen möglichen positiven Unterstützungseffekt vermuten, aber vollige Sättigung der Bindungsstellen wurde selbst dann nicht beobachtet, wenn die wässerige Phase mit Halothan gesattigt war. Die Anzahl der pro Albuminmolekul gebundenen Halothanmolekule war durch das Vorhandensein von Olsaure nicht westentlich beeinflusst. Für rote Schattenzellen und fur mit Triglyzerid angereicherte Mizellen (Chylomicrons und Lipoprotein von sehr geringer Dichte) zeigen die Absorptions-Isothermen, dass Halothan innerhalb der hydrophobischen Regionen gelöst wird. Die Verteilung von Halothan zwischen Zellen und Plasma, berechnet aus den obigen Gleichgewichts-Dialyseresultaten, stimmte mehr oder weniger mit der Verteilung im Vollblut uberein, die durch eine unabhangige Methode errechnet worden war.

SOLUBILIDAD Y DISTRIBUCION DEL HALOTANO EN LA SANGRE HUMANA

SUMARIO

Se estudiaron las interacciones del halotano con 5 constituyentes principales de la sangre humana, siguiendo una diálisis de equilibrio. Se vió que la hemoglobina, la albumina, las membranas de los glóbulos rojos y las trigliceridas contribuían significativamente a la solubilidad y, de esta forma, al transporte de halotano a lo largo de todo el sistema sanguíneo. A concentraciones fisiológicas, γ-globulin no ejerce efecto detectable alguno en la solubilidad del halotano. La absorción isoterma de la unión de halotano a la hemoglobina y a la albumina sugiere un posible efecto de cooperación positiva, pero la total saturación de los emplazamientos de unión no se llegó a observar, ni siquiera cuando la fase acuosa se saturó con halotano. El numero de moléculas de halotano unidas/molécula de albumina no se vió afectado por la presencia de ácido oléico. Para los glóbulos rojos y las micelas ricas en triglicerida (filomicrons y lipoproteínas de baja densidad), las isotermas de absorción surgirieron que el halotano se disuelve dentro de las regiones hidrofóbicas. La distribución de halotano entre las células y el plasma, que se calculó a partir de los resultados anteriormente obtenidos para la diálisis de equilibrio, coincidia de forma aceptable con la distribución en la totalidad de la sangre, que se determinó mediante un método independiente.

Br. J. Anaesth. (1980), **52**, 863

INTERACTION OF CALCIUM AND POTASSIUM WITH NEUROMUSCULAR BLOCKING AGENTS

B. E. WAUD AND D. R. WAUD

SUMMARY

Dose–response curves for blockade of the indirectly elicited twitch of isolated guineapig nerve–lumbrical muscle preparations were determined for tubocurarine and pancuronium in the presence of potassium 2, 4 and 6 mmol litre^{-1} and calcium 1, 2 and 3 mmol litre^{-1}. Increases in concentration of either ion decreased the sensitivity of the preparation to both drugs. Over the physiological range of concentrations of potassium and calcium, 36% and 27% variation in dosage can be expected.

Much information is available concerning the influence of the ionic composition of the bathing medium on the electrophysiological behaviour of the neuromuscular junction. For example, calcium has been shown to decrease the degree of depolarization produced by acetylcholine (Ginsborg and Jenkinson, 1976), to accentuate desensitization (Manthey, 1966), and to alter affinity of the receptor for tubocurarine (Jenkinson, 1960)—all postsynaptically. Calcium is known also to have a profound presynaptic effect on the release of transmitter; that is, a nerve impulse will release more acetylcholine if the concentration of calcium is increased (Katz and Miledi, 1965). However, despite this information on the action of calcium on the individual components of the system, we know neither the direction nor the extent of the overall effect. Can the increase in the release of the transmitter produced by the increase in calcium concentration override the concomitant decrease in postsynaptic chemosensitivity? More particularly, will the synapse be more or less sensitive to tubocurarine, and by how much?

A similar problem exists with regard to potassium. Very accurate measurements have been made to demonstrate the dependence of membrane potential and the reversal potential of the end-plate potential on potassium concentration (Katz, 1966). Potassium can be shown to act presynaptically to increase the frequency of miniature end-plate potentials (Ginsborg and Jenkinson, 1976), or to increase the amount of transmitter released. However, as with calcium, the system is too complex to allow deduction about the overall effect of a change in potassium concentration on the dose–response relationship of tubocurarine.

We have attempted direct determination of the dose–response curves for a competitive neuromuscular blocking agent in the presence of varying concentrations of each ion.

METHODS

The experiments were performed using an isolated guineapig nerve–lumbrical muscle preparation. The preparation was suspended in Krebs' solution (composition (mmol litre^{-1}): sodium 138; potassium 2–6; calcium 1–3, magnesium 1.22; chloride 123; dihydrogen phosphate 1.2; sulphate 1.22; bicarbonate 25; plus glucose, 2.08 g litre^{-1}) bubbled with oxygen 95%, carbon dioxide 5% and maintained at 37 °C. The nerve was placed in contact with a pair of platinum electrodes and stimulated every 10 s with a shock of 0.3 ms duration and twice maximum intensity. The resulting indirectly elicited twitch response was recorded with an isometric transducer connected to an oscillograph pen recorder.

After isolation, the preparation was equilibrated with a bathing solution of potassium 5.9 mmol litre^{-1} (the usual value for Krebs' solution) and calcium 1, 2 or 3 mmol litre^{-1}. Alternatively, the concentration of calcium was held at the customary 2.5 mmol litre^{-1} and the potassium set at 2, 4 or 6 mmol litre^{-1}. Following equilibration, tubocurarine or pancuronium was added in increasing concentrations to give a series of step-wise decreases in twitch height. The results were plotted as twitch height against concentration of antagonist. A sigmoid curve was fitted to the results by an iterative non-linear least squares technique analogous to that used previously in this

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0007–0912/80/090863–04 $01 00

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laboratory (Waud, 1975), and an estimate of the concentration halving the twitch response—the tubocurarine or pancuronium ED$_{50}$—was obtained. Finally, these ED$_{50}$ values were plotted against the concentration of potassium or calcium in which they were obtained to demonstrate the relationship of the dose of tubocurarine or pancuronium to ionic composition.

RESULTS

Figure 1 shows representative dose–response curves obtained with tubocurarine at three concentrations of potassium. There was a clear shift of the curve to the right with increasing concentrations of potassium; that is potassium increases the dose of tubocurarine required to produce any given depth of block. The results of all such experiments are presented in figure 2, with the corresponding values for pancuronium. Both drugs were affected similarly by changes in concentration of potassium.

Calcium also had a marked effect on the preparation. Figure 3 shows representative dose–response curves obtained with pancuronium at three calcium concentrations. Figure 4 summarizes the results, with the corresponding values obtained with tubocurarine. Both pancuronium and tubocurarine were affected similarly by changes in concentration of calcium.

The effects of tubocurarine and pancuronium were reversible following washing.

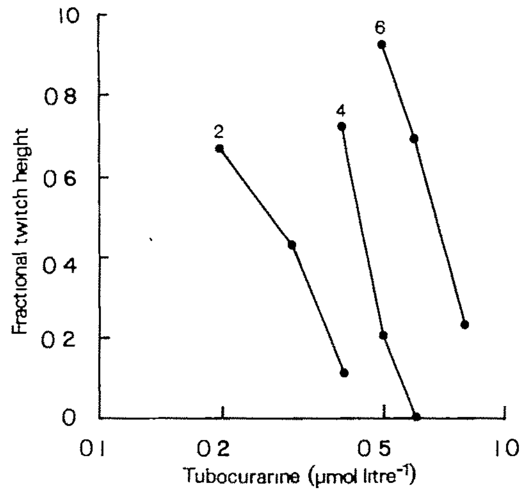

FIG. 1. Representative tubocurarine dose–response curves. Isolated guineapig nerve–lumbrical muscle preparation stimulated indirectly. Ordinates: twitch heights as fraction of control. Abscissae: concentrations of tubocurarine. From left to right the three curves represent results from three separate muscles taken from the same animal and bathed in potassium 2, 4 and 6 mmol litre^{-1} respectively.

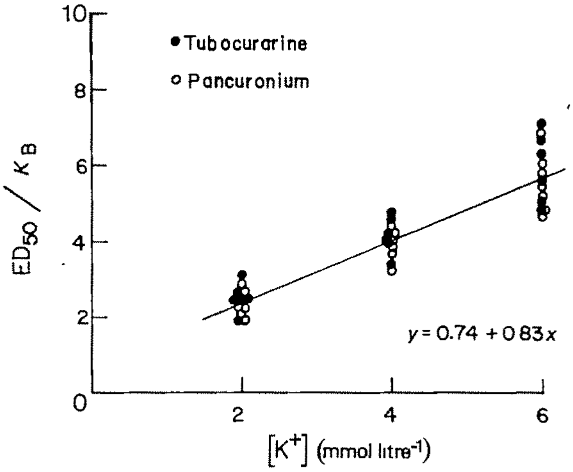

FIG. 2. Summary of relationship of tubocurarine and pancuronium ED$_{50}$ to potassium concentration. Ordinates: relaxant ED$_{50}$ values standardized on the basis of the drug–receptor dissociation constant K_B (Waud, Cheng and Waud, 1973). Such scaling eliminates potency differences between competitive blocking agents. Abscissae: potassium ion concentrations. Open circles: pancuronium; full circles: tubocurarine. Both drugs show equivalent decreases in potency as the potassium ion concentration increases. The straight line was fitted to the results by least squares.

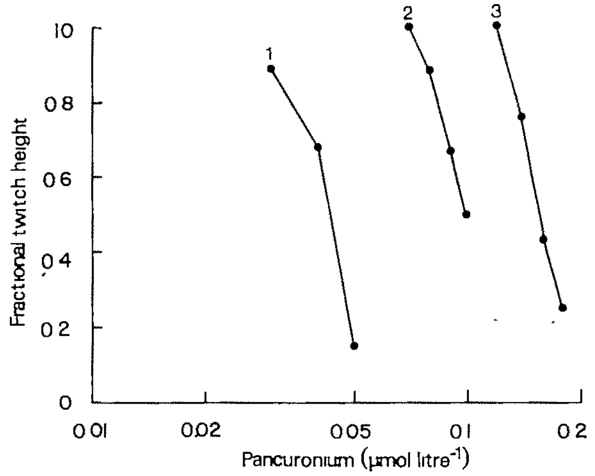

FIG. 3. Representative dose–response curves to pancuronium in the presence of three concentrations of calcium ion (1, 2 and 3 mmol litre^{-1}). Plot as in figure 1.

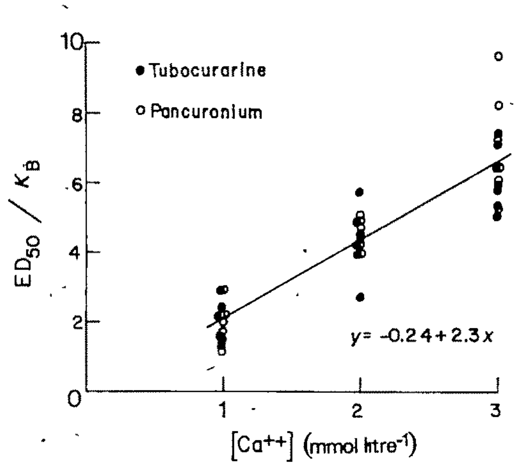

FIG. 4. Relation of relaxant ED_{50} to calcium concentration. Plot as in figure 2.

DISCUSSION

Increases in the concentration of either potassium or calcium produced decreases in the sensitivity of the isolated nerve–muscle preparation to both tubocurarine and pancuronium. These results represent the effect of relatively acute changes in concentration of the ions studied.

Each dose–response curve in figures 1 and 3 represents an experiment which took about 6 h to complete. However, it was found that with an acute change of potassium or calcium ion concentration the twitch response shifted rapidly (in a few min) to the new level. In the case of potassium, chronic changes in plasma concentration may produce different effects as the ion redistributes across the cell membrane. Calcium, on the other hand will probably show less difference with chronic changes, since intracellular concentrations appear to be actively maintained at relatively stable (and low) values.

Patients can show considerable variation in sensitivity to competitive neuromuscular blocking agents. For example, Katz (1967) gave tubocurarine 0.1 mg kg^{-1} to a group of subjects and found that the degree of block ranged from imperceptible to complete. Presumably this variation reflects the interplay of many factors such as end-organ sensitivity, pharmacokinetic processes, and the patient's physical condition. The first step in sorting out the relative contributions of such a multitude of factors is to examine the effect of each in isolation in a well-controlled system. The present study presents such information for two variables, plasma potassium and calcium ion concentrations. The use of an isolated organ preparation permits a change in the variable of interest without changing others. This may be contrasted with analogous studies *in vivo* in which, in order to change concentration of potassium, large and repeated doses of diuretics were used (Hill et al., 1978). Such studies are hard to interpret because of the difficulty in determining which of the many effects of the diuretic is responsible for the results observed.

The observations with calcium may be viewed in the framework of the extent of patient-to-patient variation in plasma concentration of this ion. A normal range of 2.1–2.6 mmol $litre^{-1}$ (Castleman, 1974) for total calcium ion concentration would (since 50% is plasma bound) correspond to 1.06–1.31 mmol $litre^{-1}$ in our Krebs' solution which contained no protein. From figure 4 this degree of variation would lead to a change of ED_{50}/K_B from 2.2 to 2.8, corresponding to about a 27% increase in ED_{50}. The wide range of ion concentration that could accompany pathological states would produce greater alteration in sensitivity to tubocurarine or pancuronium.

In the case of potassium, the normal range is of the order of 3.5–5.0 mmol $litre^{-1}$ (Castleman, 1974). Figure 2 indicates a corresponding change in dose requirement of tubocurarine or pancuronuim from 3.6 to 4.9 units of K_B or a 36% increase in ED_{50}. Again, the wider range of pathological variations in ion concentration would produce more extensive perturbation of dose requirement.

The present measurements should not be used to determine in advance the dose of a neuromuscular blocking agent, but as background information for titration of the drug against the patient's response.

ACKNOWLEDGEMENT

Supported by Grant NS 12255 from NINCDS.

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INTERACTION DU CALCIUM ET DU POTASSIUM AVEC LES AGENTS DE BLOCAGE NEUROMUSCULAIRE

RESUME

On a déterminé les courbes dose/réaction pour le blocage de la crispation produite indirectement sur des préparations de muscle/nerf lombrique isolé du cochon d'Inde pour la tubocurarine et le pancuronium en présence de potassium à raison de 2, 4 et 6 mmol litre^{-1} et de calcium à raison de 1, 2 et 3 mmol litre^{-1}. Les augmentations de concentration de l'un ou l'autre ion ont fait baisser la sensibilité de la préparation à ces deux médicaments On peut s'attendre à des variations dans le dosage de 36% et de 27% sur la plage physiologique des concentrations de potassium et de calcium.

WECHSELWIRKUNG VON KALZIUM UND KALIUM MIT NERVENMUSKEL-BLOCKIERUNGSMITTELN

ZUSAMMENFASSUNG

Es wurden Dosis–effektkurven fur die Blockade der indirekt ausgelosten Zuckungen bei isolierten nerven–lumbrikalen Meerschweinchen-Muskelpraparaten fur Tubocurarin und Pancuronium im Beisein von 2, 4 und 6 mmol Liter^{-1} Kalium und 1, 2 und 3 mmol Liter^{-1} Kalzium bestimmt. Erhohungen der Konzentration des einen oder des anderen Ions haben die Empfindlichkeit des Präparats gegenuber beiden Mitteln vermindert. Über den physiologischen Bereich von Kalium- und Kalziumkonzentrationen kann man mit Dosis-Variationen von 36% und 27% rechnen.

INTERACCION DEL CALCIO Y DEL POTASIO CON LAS AGENTES DE BLOQUEO NEUROMUSCULAR

SUMARIO

Se determinaron las curvas de respuesta-dosis para el bloqueo de la crispatura indirectamente obtenida de preparaciones musculares del nervio lumbrical de animales de laboratorio aislados, en lo que respecta a la tubocuranina y al pancuronium, en presencia de 2, 4 y 6 mol litro^{-1} de potasio y de 1, 2, 3 mol litro^{-1} de calcio. El aumento de la concentración de cualquiera de estos iones disminuyó la sensibilidad de la preparación de ambas drogas. A lo largo de la gama fisiológica de una variación del 36% al 27% en la dosis

Br. J. Anaesth. (1980), **52**, 867

ACTIVITY OF CARBONIC ANHYDRASE IN STORED BLOOD

J. PONTE, J. JOHNS, M. TARR AND C. JEYNES

SUMMARY

The activity of carbonic anhydrase in blood stored in CPD at 4 °C for up to 31 days was measured electrometrically at 5-day intervals and compared with that in fresh blood taken from four normal subjects. No change in activity in stored red cell lysates was observed over this period. There was a clear increase in activity in serum from stored blood with time. These results are discussed in the context of alveolar-to-arterial carbon dioxide gradients seen occasionally in patients following massive transfusions of stored blood.

We have observed, on occasions, that artificially ventilated patients who have received large transfusions of blood at operation (> 5 litre) developed persistently high values of arterial $P\text{CO}_2$ (> 8 kPa) in spite of a minute ventilation in excess of the predicted value for body weight and temperature and without obvious impairment of oxygen exchange. Two explanations are possible: either a substantial increase in lung physiological deadspace had occurred or there was a reduction in the carbonic anhydrase content of the infused cells leading to a diminished loss of carbon dioxide in the pulmonary capillaries. We have investigated this latter possibility since, in addition, virtually nothing is known about the fate of carbonic anhydrase in stored blood.

Although the effects of storage on such properties of red cells as the oxygen carrying capacity, the depletion of clotting factors and the ionic composition of plasma have been studied in some detail (Spielmann and Seidl, 1970; Valeri, 1976; Mollison, 1979), much less attention has been paid to the carbon dioxide-carrying capacity of blood. In particular, very little is known about the rate at which carbon dioxide is taken up and released by stored blood, reactions which will be determined largely by the presence of intracellular carbonic anhydrase which, it is believed, accelerates carbon dioxide hydration/dehydration reactions 13 000-fold (Kernohan and Forrest, 1963). The importance of carbonic anhydrase is illustrated by the estimate that at rest 78%, and in exercise 90%, of the carbon dioxide eliminated in the lungs is facilitated by the action of carbonic anhydrase (Swenson and Maren, 1978).

If carbonic anhydrase is inhibited by the action of acetazolamide in doses greater than 50 mg kg^{-1} in animals, carbon dioxide transport is obviously affected. Carbon dioxide elimination in the pulmonary capillaries is restricted to that in physical solution in plasma and, if oxygen exchange is unimpaired, to carbamino carbon dioxide. Alveolar $P\text{CO}_2$ decreases, arterial $[\text{HCO}_3^-]$ is only slightly less than mixed venous $[\text{HCO}_3^-]$ and a substantial alveolar-to-arterial $P\text{CO}_2$ gradient, usually greater than 4 kPa (30 mm Hg), develops (Tomashefski, Chinn and Clark, 1954; Cain and Otis, 1961; Bidani and Crandall, 1978). Recently, it has been shown that this gradient develops over the first 10–15 s after blood leaves the pulmonary capillaries (Carruthers, Ponte and Purves, 1980). It is anticipated that a similar picture could develop following massive blood transfusion if the carbonic anhydrase content of the stored, infused blood had been decreased significantly. The experiments described here were designed to study this possibility.

METHODS

Blood was obtained from four healthy subjects. Of the 200 ml obtained from each subject, half was stored as whole blood and the other half as packed cells, washed twice with sodium chloride 0.9 g dl^{-1}. Blood was stored in standard plastic bags in citrate phosphate dextrose (CPD) at 4 °C. Measurements of carbonic anhydrase activity were made on the 1st, 5th, 10th, 14th, 19th, 25th and 31st days of storage. Measurements were made on 7-ml samples removed

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0007-0912/80/090867-06 $01.00

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aseptically from the bags and on 10 ml of fresh blood taken from the four subjects on each of these days into heparinized syringes. All samples were analysed, before the preparation of the lysates, for $P\text{CO}_2$, $P\text{O}_2$, pH, base excess (BE), red cell count (RBC), haemoglobin content (Hb), packed cell volume (PCV), and mean haemoglobin concentration per cell (MCHC) using a Radiometer ABL2 and an automatic Coulter counter.

The activity of carbonic anhydrase was measured in diluted lysates of the red cells (1 : 10 000) and in the supernatant serum by means of an electrometric technique modified from that of Wilbur and Anderson (1948). The rate of the hydration reaction of carbon dioxide was measured with a fast responding pH electrode (Russell pH, Auchtermuchty, Fife, Scotland) with a time constant of less than 0.1 s at 27 °C. A buffer solution was prepared with MOPS buffer 0.1 mol litre^{-1} (Morpholino–propane-sulphonic acid BDH Chemicals) titrated to a pH of 7.4 with 0.1 TRIS at 37 °C. At 27 °C, the pH was 7.2. Five millilitre of whole blood was spun for 15 min and the serum separated and saved for analysis. The cells were then washed twice with sodium chloride 0.9 g dl^{-1} and 1 ml of cells diluted with 9 ml of distilled water and left to lyse for 5 min. The clear lysate, after further spinning, was diluted further in the buffer solution to a concentration of 10^{-3} of the original. This final dilution was verified in a colorimeter with the appropriate filter for oxyhaemoglobin and if necessary small adjustments were made in order to obtain the same readings between fresh and stored blood from the same individual. In this way, we avoided errors resulting from dilution and from the different behaviour of stored cells with centrifugation caused by changes in rigidity and shape (Sirs, 1968). One millilitre of this diluted lysate was diluted further with 9 ml of buffer (final dilution 10^{-4}) and this was contained in a small cuvette which was stirred continuously and maintained at 27 °C and in which the pH electrode and a constantin thermocouple were placed (fig. 1).

When the outputs of the electrode and thermocouple, recorded on a Watanabe multi-channel potentiometric recorder, were steady, 0.2 ml of distilled water equilibrated with 100% carbon dioxide was added suddenly to the contents of the cuvette and the rate of change of pH measured. The maximum change in pH recorded was 0.4 units: there were no changes in temperature. This procedure was repeated with the addition of 1 ml of serum instead of lysate obtained with the first centrifugation.

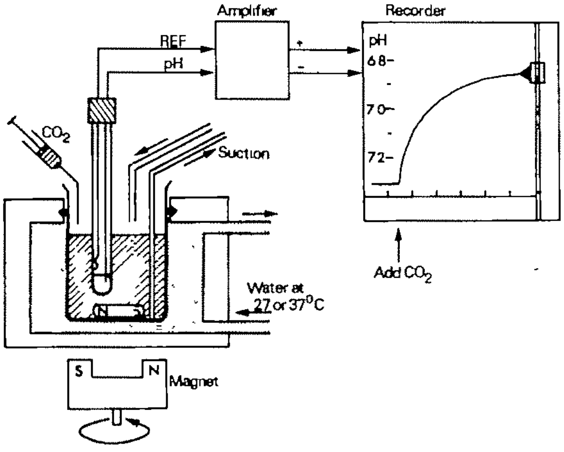

FIG. 1. Diagram of the experimental set up for the electrometric measurement of carbonic anhydrase activity. The thermocouple is not represented.

In addition, at the end of each day, the temperature of the cuvette was increased to 37 °C and the procedure repeated for the lysate from one of the subjects.

The change in pH (Y_t) in millivolts was measured at 2-s intervals after the addition of the carbon dioxide solution for up to 16 s, by which time the reaction was usually complete. This was shown to be represented by an exponential curve of the form $Y_t = Y_{\max} \cdot (1 - e^{-kt})$ because a plot of $\ln (Y_{\max}/Y_{\max} - Y_t)$ against t resulted in a straight line in all runs indicating a first order process with a rate constant, k. For convenience, this rate constant was taken as the index of enzymatic activity for the comparison of the results in fresh and stored blood.

In preliminary experiments as a test of the method, various dilutions of purified bovine carbonic anhydrase (Sigma Chemicals) were prepared and a linear relationship was obtained between the natural logarithm of the dilution and the rate constant at 27 °C. The inverse value of k is the time constant of the reaction, which was found to be 15.1 s at 27 °C and 6.4 s at 37 °C for the uncatalysed hydration reaction. For the purpose of our experiment, we saw no advantage in expressing the results in terms of the enzyme content of the red cell.

RESULTS

The values for haemoglobin concentration, mean corpuscular concentration and base excess for the blood stored up to 31 days from the four subjects are given in table I.

TABLE I. *Variables in blood against time for four subjects. (Hb = haemoglobin (g dl⁻¹); MCHC = mean haemoglobin concentration per cell (g dl⁻¹); BE = base excess (mmol litre⁻¹))*

	J.P.			J.J.			M.T.			J.U.		
Day	Hb	MCHC	BE	Hb	MCHC	BE	Hb	MCHC	BE	Hb	MCHC	BE
Stored blood												
1	11.2	34.0	−20.2	13.5	34.6	−20.1	13.2	33.7	−22.1	11.0	33.5	−23.5
5	11.3	33.5	−24.8	13.3	33.6	−22.8	12.5	33.4	−29.6	11.1	33.1	−25.2
10	10.9	32.2	−28.3	11.6	32.6	−25.4	12.1	34.4	−32.2	12.2	31.4	−33.4
14	11.3	33.7	−30.9	12.4	34.0	−33.2	11.6	33.2	−33.4	10.5	32.7	−33.2
19	11.1	34.5	−33.5	12.6	34.3	−33.6	11.6	35.0	−36.2	10.2	33.0	−35.4
25	10.9	33.2	−36.5	13.5	33.1	−40.6	11.7	33.1	−39.1	10.2	33.4	−37.8
31	11.6	32.8	−40.0	12.6	32.7	−43.6	12.1	32.4	−43.4	10.2	31.2	−40.1
Mean	11.19	33.41	−30.6	12.79	33.56	−31.73	12.11	33.60	−33.71	10.77	32.61	−32.66
SD	0.23	0.38	6.3	0.64	0.38	8.42	0.53	0.69	6.36	0.68	0.87	5.73
Fresh blood												
Mean	14.07	34.03	1.36	15.48	34.78	−0.54	15.82	33.98	0.0	13.32	33.71	−1.94
SD	0.36	0.67	0.76	0.56	0.89	1.44	0.18	0.85	0.98	0.48	0.87	1.08

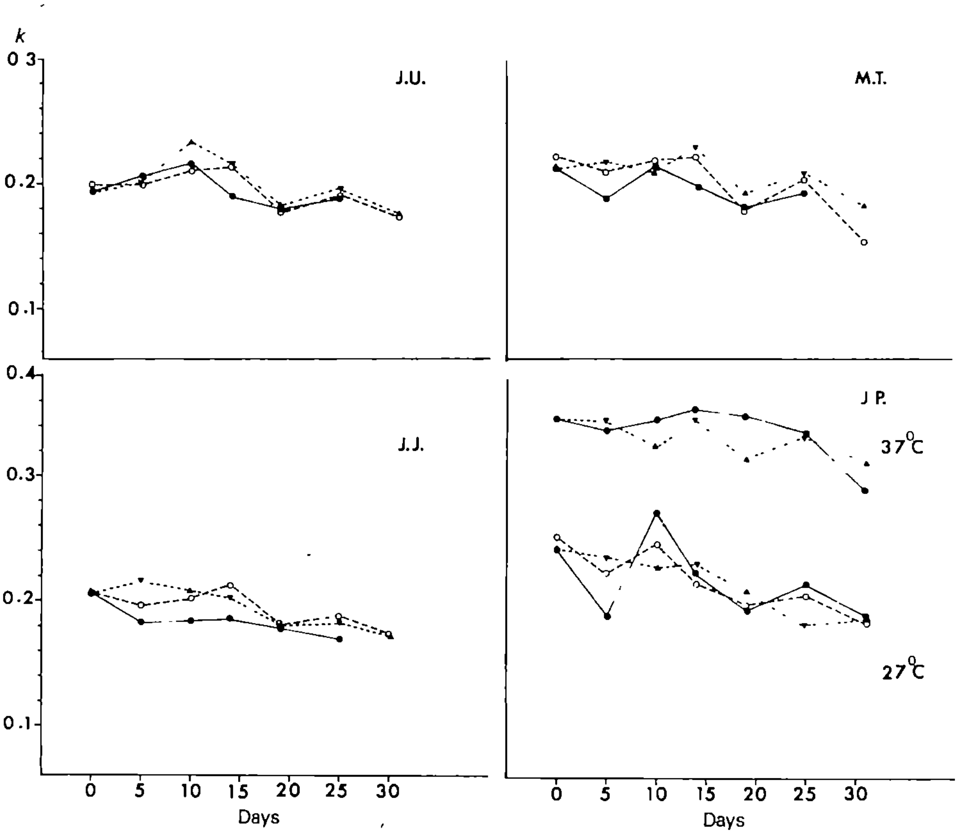

FIG. 2. Plots of reaction rate constant *k* against duration of storage (days) for the four subjects. Solid circles are for fresh blood lysates, open circles for stored packed cells, and triangles for stored whole blood.

TABLE II. *Summary of values for* k, *the rate constant for four subejcts, and the uncatalysed reaction*

	Subject					Uncatalysed	
	J.P. (37 °C)	J.P. (27 °C)	J.J.	M.T.	J.U.	27 °C	37 °C
Fresh blood							
Mean	0.339	0.219	0.184	0.198	0.196	0.066	0.156
SD	0.021	0.029	0.011	0.013	0.024	0.004	0.007
Stored blood							
Mean	0.333	0.216	0.195	0.208	0.200	—	—
SD	0.014	0.022	0.016	0.015	0.018	—	—
Stored packed cells							
Mean	—	0.219	0.194	0.201	0.195	—	—
SD	—	0.023	0.013	0.024	0.015	—	—

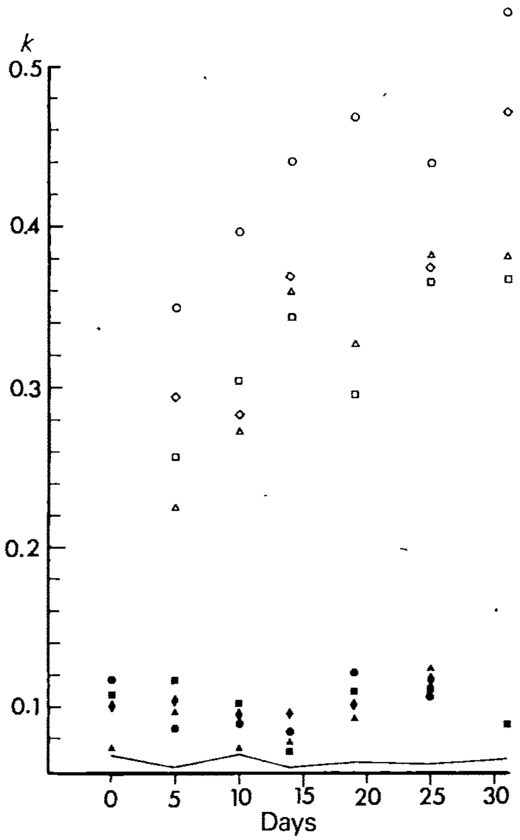

FIG. 3. Reaction rate constant *k* against duration of storage (days) for the serum of fresh (solid symbols) and stored (open symbols) blood of the four subjects, represented by different symbols. The solid line represents the rate constant of the uncatalysed reaction at the same temperature (27 °C).

Large negative base excess and small haemoglobin values compared with fresh blood were observed, presumably as a result of the addition of CPD. Base excess values became progressively more negative with time, as has been observed previously by Prins and Loos (1970).

Plots of the rate constant, *k*, against the duration of storage are shown in figure 2 for the four subjects at 27 °C and, in addition, for one subject at 37 °C. Means and standard deviations appear in table II.

In each plot, values for the rate constant on each date of sampling are given for fresh blood, stored blood and stored packed cells. No consistent differences for these values were observed for any subject and no changes were observed with time.

In figure 3, the rate constant is again plotted against the duration of storage. The mean values of *k* for the uncatalysed reaction at 27 °C are shown as the solid line at the bottom of the figure. Activity in the serum of fresh blood (solid symbols) for the four subjects was negligible, but activity in the serum of stored blood (open symbols) increased progressively with time. This indicates either progressive haemolysis or increased susceptibility of the stored red cells to the effects of centrifugation.

DISCUSSION

In this study, we found no evidence that the activity of carbonic anhydrase in red cells decreases appreciably with storage of blood up to 31 days. We have not applied tests of statistical significance to the plots shown in figure 2, since there was clearly no loss of activity of any clinical importance.

The effects of storage of blood upon other intracellular enzymes have been studied in some detail by other workers, but only some have been found to be decreased (Blum, 1970). Carbonic anhydrase is present in the form of two main iso-enzymes in human red cells which are distinguishable by immunological techniques. Their catalytic activity is slightly different and their relative proportion varies by a small amount with ageing of cells *in vivo* (Funakoshi and Deutsch, 1971). Carbonic anhydrase concentrations are much smaller in the red cells of the newborn (Mondrup and Anker, 1975) and are increased in a number of pathological states (Mondrup and Anker, 1976). It has been found that thyroid hormones (Kondo et al., 1978) and hydrocortisone (Russell, Loesebrink and Chernick, 1976) affect the amount of enzyme in the red cells. The activity of the normal enzyme is altered in the presence of phosphate compounds (Narumi and Miyamoto, 1974) and various anions (Maren, Rayburn and Liddell, 1976). It is probable, however, that most of these studies have limited clinical significance.

Since the discovery and characterization of carbonic anhydrase by Meldrum and Roughton in 1933, the physiological significance of the apparent abundance of the enzyme within the red cell has puzzled many workers (Maren, 1967) since the absence of the enzyme seems to be compatible with life, certainly at rest (Mondrup and Anker, 1975). However, Swenson and Maren (1978) have cautioned that this may not be so if there is a large increase in metabolic demand as in exercise. However, in the intact subject it appears that red cells are not the only site of carbonic anhydrase involved in carbon dioxide elimination in the lung, since it has been shown recently that carbonic anhydrase in or close to, the pulmonary capillary endothelium catalyses carbon dioxide dehydration reactions in plasma (Crandall and O'Brasky, 1978; Effros, Chang and Silverman, 1978; Klocke, 1978). The use of dilute lysates thus seems to be an acceptable way of predicting the changes in activity which would occur both in plasma and with the higher concentrations of the enzyme inside the red cells (Kernohan and Forrest, 1963; Forster and Itada, 1979).

In conclusion, our results do not support the hypothesis that carbonic anhydrase activity is impaired in patients who received large transfusions of stored blood, but questions relating to carbon dioxide transport and elimination in such patients deserve further investigation.

ACKNOWLEDGEMENTS

The authors thank Dr M. J. Purves for providing facilities in the department of Physiology and for helpful discussion and Dr A. Frazer of the Haematology Department, Southmead Hospital, for advice and facilities for collection and storage of blood. This work formed part of the requirements for the degree of B.SC. (J. J. and M. T.). The views expressed are personal to M. T. and not necessarily those of the Royal Navy.

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ACTIVITE DE L'ANHYDRASE CARBONIQUE DANS LE SANG ENTREPOSE

RESUME

L'activité de l'anhydrase carbonique se produisant dans le sang entreposé dans du CPD (citrate-phosphate-dextrose) à 4 °C pendant une période allant jusqu'à 31 jours a été mesurée électrométriquement à des intervalles de 5 jours et comparée avec celle se produisant dans du sang frais prélevé sur quatre sujets normaux. On n'a observé au cours de cette période aucun changement dans l'activité des lysates des globules rouges entreposés. Il y a eu avec le temps une très nette croissance de l'activité se produisant dans le sérum du sang entreposé. Ces résultats sont débattus dans le contexte des gradients du gaz carbonique alvéolaire/artériel que l'on voit occasionnellement sur des malades après des transfusions massives de sang entreposé.

DIE AKTIVITÄT VON KOHLENANHYDRASE IN GESPEICHERTEM BLUT

ZUSAMMENFASSUNG

Die Aktivität von Kohlenanhydrase in Blut, das übereinen Zeitraum von bis zu 31 Tagen bei 4 °C in Zitrat-Phosphat-Dextrose aufbewahrt wurde, wurde in Intervallen von 5 Tagen electrometrisch bestimmt und mit der Aktivität in frischem Blut aus vier gesunden Versuchspersonen verglichen. Über diesen Zeitraum hinweg wurde bei den gespeicherten Rotkörperchen-Lysaten keine Änderung der Aktivität beobachtet. Mit der Zeit wurde eine deutliche Zunahme der Aktivität bei Serum aus gespeichertem Blut beobachtet. Diese Ergebnisse werden in Zusammenhang mit Kohlendioxyd-Gefällen zwischen Alveoli und Arterien besprochen, wie sie gelegentlich nach massiven Transfusionen von gespeichertem Blut beobachtet werden

ACTIVIDAD DEL ANHIDRIDO CARBONICO EN LA SANGRE ALMACENADA

SUMARIO

Se midió electrométricamente la actividad del anhidrido carbónico en la sangre almacenada en CPD (citrato-fosfato-dextrosa) a 4 °C por espacio de hasta 31 días, a intervalos de 5 dias, y se comparó con la de sangre fresca extraida de 4 sujetos normales. No se observó cambio alguno en la actividad de los lisatos almacenados a lo largo de este periodo. Hubo un claro incremento de la actividad en el suero de la sangre almacenada, a lo largo del tiempo. Estos resultados se discuten en el contexto de los gradientes de dióxido de carbono alveolar-a-arterial que se ven de forma ocasional en pacientes que siguen trasnfusiones masivas de sangre almacenada.

Br. J. Anaesth. (1980) **52**, 873

I.V. LIGNOCAINE IN REFLEX AND ALLERGIC BRONCHOCONSTRICTION

H. DOWNES, N. GERBER AND C. A. HIRSHMAN

SUMMARY

The protection against bronchospasm afforded by infusions of lignocaine was tested in dogs anaesthetized with thiamylal by challenge with aerosols of citric acid (CAA) or ascaris antigen (AAA). During the infusion of lignocaine, the response to CAA was blocked or markedly attenuated, but AAA still elicited a large increase in pulmonary resistance (R_L). In untreated dogs, CAA increased R_L from 0.14 ± 0.05 (mean ± SEM) kPa litre^{-1} s to 1.09 ± 0.18, whereas in dogs treated with lignocaine, R_L was 0.19 ± 0.09 before challenge with CAA and 0.44 ± 0.13 after challenge. AAA increased R_L from 0.14 ± 0.06 kPa litre^{-1} s to 3.01 ± 0.65 in untreated dogs, and from 0.34 ± 0.10 kPa litre^{-1} to 1.85 ± 0.69 in dogs treated with lignocaine. Blood concentrations of lignocaine were 1.5 ± 0.3 and 2.5 ± 0.6 µg ml^{-1} during challenge with CAA and AAA, respectively. We conclude that lignocaine, at blood concentrations which will reduce the risk of cardiac arrhythmia, markedly reduces reflex bronchoconstriction, but has relatively little effect on that initiated by allergic mediators.

The i.v. administration of local anaesthetic agents has been used to treat bronchospasm occurring in both awake (Dos Ghali, Bourdin and Guiot, 1943a, b; Durieu, De Clercq and Duprez, 1946) and anaesthetized man (Brandus et al., 1970). Lignocaine by this route has been shown to depress the cough reflex in anaesthetized man (Steinhaus and Howland, 1958; Steinhaus and Gaskin, 1963), but parallel effects on pulmonary mechanics were not measured. Moreover, since bronchospasm occurring during anaesthesia may have different causes, the efficacy of lignocaine in treating bronchospasm may depend critically on the nature of the initiating stimulus. Therefore, in dogs anaesthetized with barbiturates, we undertook to test the protection afforded by the i.v. administration of lignocaine against bronchospasm initiated by a chemical irritant (citric acid aerosol, CAA) and by an antigen (ascaris antigen aerosol, AAA).

METHODS

Five Basenji–Greyhound (B–G) crossbreed dogs, each about 20 kg, were selected for these experiments on the basis of large and consistent responses during repeated challenges with CAA and AAA. Each dog served as its own control, and on different days, about 1 week apart, was challenged with CAA or AAA, with or without lignocaine treatment. The dogs were not premedicated and were anaesthetized standing, supported by a sling. After the induction of anaesthesia with thiamylal 12 mg kg^{-1} i.v., neuromuscular blockade was produced with suxamethonium and the trachea intubated with an 8.5–9 mm cuffed tracheal tube. The lungs were ventilated manually with oxygen 100%. Additional increments of thiamylal and suxamethonium were administered as required. A balloon (Dynasciences, Blue Bell, Pa.) was placed in the oesophagus under direct vision and positioned at the point where recorded end-expiratory pressure was least. The balloon contained 0.8 ml of air. A separate catheter, connected to suction, was placed in the oesophagus to keep it empty of air and liquid.

For measurement of pulmonary resistance (R_L) and dynamic compliance (C_{dyn}), the lungs were ventilated for approximately 30 s with a piston-type ventilator (Harvard Apparatus Company, Millis, Ma.) from which the inspiratory and expiratory valves had been removed. The ventilator was set to deliver a tidal volume of 400 ml at a frequency of 15 b.p.m., and produced a regular sinusoidal flow pattern with a peak inspiratory flow equivalent to $2\pi f \times 200$ ml s^{-1}. Transpulmonary pressure (P_{tp}) was measured with a differential pressure transducer (Hewlett–Packard 270) connected to the oesophageal balloon and to a needle inserted into the endotracheal tube. Airflow ($\dot{V}$) was measured with a calibrated pneumotachograph head (Hewlett–Packard 21071B) and a differen-

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0007-0912/80/090873-07 $01.00

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tial pressure transducer (Hewlett-Packard 47304A). Pressure and flow signals were recorded on a Hewlett-Packard 7754B recorder.

C_{dyn} was calculated by dividing tidal volume by the difference in pressure between points of zero flow. P_{tp} was measured at the point of maximum inspiratory flow. With the sinusoidal pattern used, this occurred exactly halfway through the inspiratory cycle and corresponded to an inspiratory volume of 200 ml above functional residual capacity. Pulmonary elastic pressure at this point was calculated by dividing 200 ml by compliance. Pressure required to overcome flow resistance (P_{res}) was calculated by subtracting elastic pressure from P_{tp}. Total resistance was then calculated by dividing P_{res} by instantaneous $\dot{V}$ at this point. R_L was obtained by subtracting the resistance of the tracheal tube from this value. All volumes were corrected to BTPS. R_L and C_{dyn} were calculated from a mean of seven consecutive breaths. The electrocardiogram was monitored throughout with a Grass 79 recorder.

Aerosols were delivered by a Hudson 3000 nebulizer driven by compressed oxygen and inserted between the inspiratory limb of a circle anaesthesia system and the tracheal tube. To avoid residual contamination, the circle system was changed after completion of aerosol administration. Ascaris antigen was prepared by Sephadex filtration using the method of Mackler, Malley and Amkraut (1971). Ascaris protein, 30 μg of the purified extract, was placed in 10 ml of water and delivered as an aerosol over a 10-min period. Citric acid aerosols were made up in distilled water and delivered for 2 min. The most reactive animal was challenged with 3% citric acid and the remaining four animals with 10% citric acid. R_L and C_{dyn} were measured immediately at the end of the administration of the aerosol and at 5-min intervals for 30 min.

During the lignocaine studies, following induction of anaesthesia, a loading dose of lignocaine 1.8 mg kg^{-1} was administered i.v. over 1 min. Thereafter, maintenance infusion rates of 4–6.5 mg kg^{-1} h^{-1} were administered throughout the experimental period. At 25 min after the start of the maintenance infusion of lignocaine, baseline values for R_L and C_{dyn} were measured; and at 30 min the dogs were challenged with AAA and CAA.

For determination of blood lignocaine concentrations, 2 ml of blood was withdrawn from an indwelling catheter in the cephalic vein and added directly to a tube containing 1-chlorobutane 30 ml and 1 ml of phosphate buffer 0.1 mol $litre^{-1}$ (pH 7.4) with 50 units of heparin. After shaking for 10 min followed by centrifugation, a 25-ml portion of the organic layer was extracted into 2 ml of hydrochloric acid 1 mol $litre^{-1}$. A 1.6-ml aliquot of the acid was neutralized with 2.5 ml of phosphate buffer 4 mol $litre^{-1}$ (pH 7.4) in a Reactivial and extracted into chloroform 25 μlitre containing docosane 50 μg ml^{-1} as the internal standard. Samples were analysed on a Hewlett-Packard 5830 gas chromatograph using flame ionization and a 1.75 m × 2 mm (i.d.) glass column packed with 1.5% OV-101 on Gas Chrom Q. The oven temperature was programmed at 10 °C min^{-1} from 170 to 250 °C. Standard curves were prepared for each experiment by adding lignocaine to dog blood; correlation coefficients for standard curves varied from 0.991 to 0.998.

R_L and C_{dyn} during lignocaine infusions were compared with appropriate controls at each time interval by a paired t test (Steele and Torrie, 1960), at the $P > 0.05$ level of significance.

RESULTS

In untreated dogs (fig. 1), inhalation of CAA produced large increases in R_L and decreases in C_{dyn}, which were maximal at 5 min after completion of the aerosol challenge (7 min after the start). R_L increased from a pre-challenge control of 0.14 ± 0.05 (mean ± SEM) kPa $litre^{-1}$ s to 1.09 ± 0.18 at 5 min after challenge, and C_{dyn} decreased from 1400 ± 270 ml kPa^{-1} pre-challenge to 520 ± 80 at 5 min after challenge. In individual animals, the change in R_L represented a 3- to 14-fold increase.

During the infusion of lignocaine (fig. 1), the response to CAA was blocked or markedly attenuated. R_L was 0.19 ± 0.09 kPa $litre^{-1}$ s in the pre-challenge control and 0.44 ± 0.13 at 5 min after challenge, and C_{dyn} was 1600 ± 480 ml kPa^{-1} pre-challenge and 1000 ± 300 at 5 min after challenge. Four of five dogs showed either no increase in R_L or an increase of less than 1.3-fold; in the fifth dog, R_L increased by 3.5-fold (compared with a 6-fold increase without lignocaine treatment). In treated compared with untreated dogs, values of R_L after challenge were significantly less during lignocaine infusion throughout the experimental period, and C_{dyn} during lignocaine infusion was significantly greater for 20 min after challenge. Blood concentrations of lignocaine averaged 1.5 ± 0.3 μg ml^{-1} at the start of CAA and were maintained at this value for the duration of the experiment (fig. 1).

Challenge with AAA elicited large changes in R_L and C_{dyn} in both untreated and lignocaine-treated

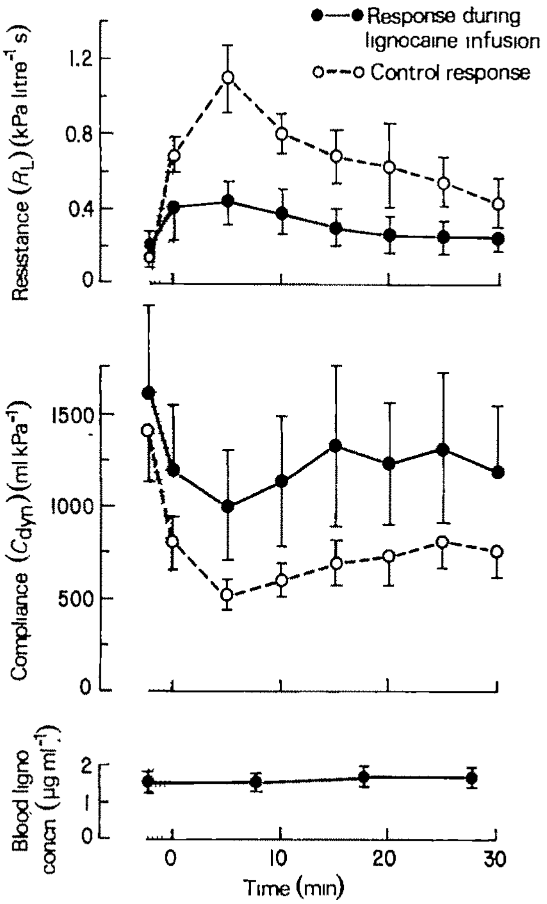

FIG. 1. Response to CAA in the same dogs, without lignocaine (ligno.) treatment (○--○) and during lignocaine infusion (●—●). Each point represents the mean for five dogs and SEM. Time (min) after completion of the aerosol challenge; period of application of the aerosol is indicated by the shaded bar.

dogs (fig. 2). These changes were maximal immediately after completion of the aerosol challenge (10 min after its start). In untreated dogs, AAA increased R_L from a pre-challenge control of 0.14 ± 0.06 kPa litre^{-1} s to 3.01 ± 0.65 immediately after challenge, and decreased C_{dyn} from 1746 ± 445 ml kPa^{-1} pre-challenge to 372 ± 166 immediately after challenge. During the infusion of lignocaine, AAA increased R_L from a pre-challenge control of 0.34 ± 0.10 kPa litre^{-1} s to 1.85 ± 0.69 immediately after challenge, and decreased C_{dyn} from 1076 ± 240 ml kPa^{-1} pre-challenge to 434 ± 123 immediately after challenge. After challenge with AAA, there was no significant difference in C_{dyn} between lignocaine-treated and untreated dogs, but R_L was significantly less in the lignocaine-treated dogs for the first 10 min after challenge. Blood concentrations of lignocaine averaged 2.5 ± 0.6 μg ml^{-1} at the start of AAA and were maintained close to this value for the duration of the experiment (fig. 2).

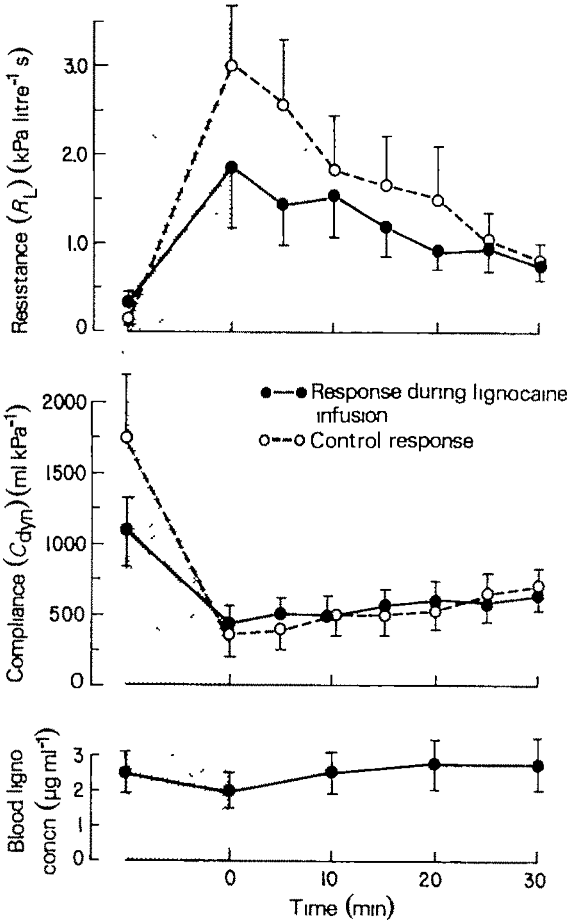

FIG. 2. Response to AAA in the same dogs, without lignocaine (ligno.) treatment (○--○) and during lignocaine infusion (●—●). Each point represents the mean for five dogs and SEM. Time (min) after completion of the aerosol challenge; period of application of the aerosol is indicated by the shaded bar.

DISCUSSION

Local anaesthetics have been used sporadically in the treatment of bronchospasm, beginning with cocaine before the turn of the century (Mosler, 1886). Although cocaine was reported to be highly effective in asthma (Potter, 1906), at least in comparison with other treatments then in use, its bronchodilator effects may have reflected sympathomimetic rather than anaesthetic actions. This explanation would not apply for procaine, which was given i.v. to treat bronchospasm associated with asthma or pulmonary embolism (Dos Ghali, Bourdin and Guiot, 1943a, b) or during anaesthesia (Brandus et al., 1970), and was an ingredient of commercially produced bronchodilator aerosols (Dautrebande, 1962). These older reports do not include direct measures of drug effect on pulmonary mechanics.

More recently, local anaesthetic aerosols have been shown to block a variety of airway reflexes (Jain et al., 1973; Dain, Boushey and Gold, 1975; Cross et al., 1976), presumably by topical anaesthetic effects. Such effects could lessen the reflex component of an asthmatic attack, but lignocaine aerosols frequently elicit bronchoconstriction in patients with reactive airway disease (Miller and Awe, 1975; Weiss and Patwardhan, 1977; Fish and Peterman, 1979). This has been attributed to reflex bronchoconstriction resulting from the irritant effect of lignocaine solution (Miller and Awe, 1975; Fish and Peterman, 1979) or to prostaglandin release and displacement of membrane-bound calcium ion (Weiss and Patwardhan, 1977). Apart from these adverse effects, a portion of the reflex block by local anaesthetic aerosols could represent a systemic effect.

I.v. lignocaine, at doses comparable to those used to treat cardiac arrhythmia, has been shown to depress markedly the cough response elicited in anaesthetized patients by mechanical stimulation (Steinhaus and Howland, 1958; Steinhaus and Gaskin, 1963) or in awake patients by inhalation of CAA (Poulton and James, 1979), but parallel effects on R_L and C_{dyn} have not been well documented. Weiss and Patwardhan (1977), studying conscious asthmatic patients with stable disease, noted a slight improvement in FVC and FEV_1 following i.v. lignocaine, but Loehning, Waltemath and Bergman (1976), studying anaesthetized non-asthmatic subjects, found that i.v. lignocaine did not block the increase in R_L elicited by water aerosols. Both of these studies tested i.v. lignocaine against bronchospasm of relatively mild intensity. In contrast, Brandus and colleagues (1970) reported marked improvement, by clinical standards, following treatment, with i.v. lignocaine, of a case of severe bronchospasm occurring during anaesthesia.

In the B–G dog, inhalation of CAA or AAA elicits large changes in pulmonary mechanics of the magnitude seen in severe asthma in man. The response to CAA is primarily reflex bronchospasm and can be blocked or markedly attenuated by atropine. The response to AAA can be attributed to chemical mediators released from sensitized cells on contact with antigen. Such mediators can initiate bronchospasm directly by action on bronchial smooth muscle and indirectly by stimulation of irritant receptors with subsequent reflex bronchospasm (Drazen, 1977). In some dogs, reflex bronchospasm is the major component and the response to AAA can be blocked with atropine (Gold, Kessler and Yu, 1972). This is not true of the B–G dog, since in other studies (in the same animals) pretreatment with large doses of atropine (0.2 mg kg^{-1} i.v.) only reduced the response to AAA by about one-third, and R_L was still increased by a factor of six to 26.

Lignocaine i.v. could protect against bronchospasm by three general mechanisms: by direct effects on airway smooth muscle, by inhibition of mediator release, and by interruption of reflex arcs. *In vitro* studies (Weiss, Anderson and O'Brien, 1975; Downes and Loehning, 1977; Weiss, Hargraves and Viswanath, 1978) indicate that the first two mechanisms are possible, given an adequate drug concentration. However, the drug concentrations that produce pronounced effects *in vitro* are about one-hundred times greater than the blood lignocaine concentrations which can be achieved safely *in vivo*. Nevertheless, since lignocaine is concentrated in the lung (Sung and Truant, 1954; Keenaghan and Boyes, 1972; Benowitz et al., 1974), possibly in mast cells granules, some effect on mediator release might be achieved with i.v. administration.

In our dogs, lignocaine infusions consistently reduced the response to AAA, but the protection was slight and similar to that observed with atropine. Therefore, our studies do not indicate a marked effect of i.v. lignocaine, if any, on mediator release or on smooth muscle response to allergic mediators. Such protection as was observed probably represents interruption of reflex bronchospasm. Since the blood concentrations of lignocaine during challenge with AAA averaged 2.5 $\mu g\ ml^{-1}$ (fig. 2), or about mid-range of safe antiarhythmic concentrations (Bochner et al., 1978), a large increase in dose is not possible.

Although blood concentrations of lignocaine during challenge with CAA were slightly less (1.5 $\mu g\ ml^{-1}$), they were adequate to block or markedly reduce the irritant response. Since lignocaine at the concentrations circulating in blood has little or no anticholinergic effect on airway smooth muscle (Downes and Loehning, 1977) or local anaesthetic effect on peripheral nerve (Heavner and de Jong,

1974) we presume that the site of action is within the central nervous system.

In summary, our results indicate that lignocaine at non-toxic blood concentrations significantly reduces the intensity of reflex bronchospasm. Since topical application of lignocaine for intubation or bronchoscopy often results in blood concentrations similar to those achieved here (Bromage and Robson, 1961; Telivuo, 1965; Pelton et al., 1970; Chu et al., 1975; Viegas and Stoelting, 1975; Karvonen et al., 1976; Scott et al., 1976; Smith, 1976; Boye and Bredesen, 1979), topical anaesthesia of the airway may alter pulmonary mechanics by more than local actions. Finally, in the treatment of bronchospasm during anaesthesia, lignocaine i.v. reduces reflex bronchospasm in addition to its antitussive and antiarhythmic effects, but probably has little or no direct action on the release of allergic mediators or on the responsiveness of smooth muscle to such mediators.

ACKNOWLEDGEMENTS

The authors with to thank A. Malley, PH.D. of the Oregon Regional Primate Center for purifying the ascaris antigen, the Hudson Instrument Company of Temecula, California for supplying the nebulizer, M. Lall and F. Cetinich for typing the manuscript, B. Bonn for help with chemical assays, and D. R. Morrow for help with animal experiments.

This study was supported by NIH Grant RO1 GM 24524 and the Department of Anesthesiology Research and Education Society.

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PERFUSION DE LIGNOCAINE CONTRE LA BRONCHOCONSTRICTION REFLEXE ET ALLERGIQUE

RESUME

On a testé sur des chiens anesthésiés au thiamylal la protection qu'offrent, contre les bronchospasmes, les perfusions de lignocaine par épreuve avec des aérosols d'acide citrique (AAC) ou d'antigène ascaricide (AAA) Pendant la perfusion de lignocaine, la réaction à l'AAC a été bloquée ou nettement atténuée, mais l'AAA a continué à provoquer une forte augmentation de la résistance pulmonaire (R_{L}). Chez les chiens non traités, l'AAC a accru la R_{L} de 0,14±0,05 (moyenne±écart type des moyennes) kPa litre^{-1} s à 1,09±0,18 tandis que chez les chiens traités à la lignocaine, la R_{L} a été de 0,19±0,09 avant l'épreuve à l'AAC et de 0,44±0,13 après l'épreuve. L'AAA a accru la R_{L} de 0,14±0,06 kPa litre^{-1} s à 3,01±0,65 chez les chiens non traités, et de 0,34±0,10 kPa litre^{-1} s à 1,85±0,69 chez les chiens traités à la lignocaine. Les concentrations de lignocaine dans le sang étaient respectivement de 1,5±0,3 et de 2,6±0,6 µg ml^{-1} pendant les épreuves à l'AAC et au AAA. Nous en avons conclu qu'aux concentrations dans le sang permettant de réduire les risques d'arythmie cardiaque, la lignocaine diminue considérablement la bronchoconstriction réflexe, mais qu'elle n'a que très peu d'effet sur la bronchoconstriction créée par des médiateurs alergiques.

INTRAVENOSES LIGNOCAIN FÜR ALLERGISCHE UND REFLEX-BRONCHIALVERENGUNG

ZUSAMMENFASSUNG

Schutz gegen Bronchialkrampf durch Lignocain-Infusionen wurde an Hunden getestet, die mit Thiamylal narkotisiert waren, und die mit Zitronensaure (CAA) oder Ascarides-Antigen (AAA) besprüht wurden. Wahrend der Infusion war die Reaktion auf CAA blockiert oder deutlich abgeschwächt, aber AAA führte immer noch zu einem starken Anstieg des Lungenwiderstandes (R_{L}). Bei unbehandelten Hunden wurde R_{L} durch CAA von 0,14±0,05 (mittel±SEM) kPa Liter^{-1} s auf 1,09±0,18 erhoht, wahrend in den mit Lignocain behandelten Hunden R_{L} vor Reizung durch CAA 0,19±0,09 betrug, und 0,44±0,13 nach der Reizung. AAA erhöhte R_{L} von 0,04±0,06 kPa Liter^{-1} s auf 3,01±0,65 bei unbehandelten Hunden, und von 0,34±0,10 kPa Liter^{-1} s auf 1,85±0,69 bei Behandlung mit Lignocain. Lignocain-Blutkonzentrationen betrugen jeweils 1,5±0,3 und 2,6±0,6 µg ml^{-1} wahrend der Reizung mit CAA und AAA. Wir folgern, dass Lignocain deutlich die Gefahr des Reflex-Bronchialkrampfes verringert, aber relative wenig Wirkung auf den durch Allergie hervorgerufenen Bronchialkrampf hat.

LIGNOCAINA EN BRONCOCONSTRICCION ALERGICA Y DE REFLEJO

SUMARIO

La protección contra el espasmo bronquial que presentan las infusiones de lignocáina se comprobó en perros anestesiados con tiamilal, en contraposición a los atomizadores de ácido círico (CAA) o de antigeno ascaris (AAA). Durante la infusión de lignocaina, la respuesta a CAA quedó bloqueada o marcadamente atenuada, pero consiguió aun un gran incremento de la resistencia pulmonar (R_{L}). En el caso de los perros sin tratamiento, CAA incrementó la R_{L} desde 0,14±0,05 (media±desviación típica) kPa litro^{-1} s hasta 1,09±0,18, mientras que para los perros bajo tratamiento con lignocaina, R_{L} fue de 0,19±0,09 antes de usar CAA y 0,44±0,13 después de su uso. El uso de AAA incrementó la R_{L} desde 0,14±0,06 kPa litro s^{-1} hasta 3,01±0,65 para los perros sin tratamiento, y desde 0,34±0,10 kPa litro s^{-1} hasta 1,85±0,69 en los perros tratados con lignocaina. Las concentraciones sanguíneas de lignocaina fueron de 1,5±0,3 y de 2,6±0,6 µg ml^{-1} durante el tratamiento con CAA y AAA, respectivamente. La conclusión es, por lo tanto, que la lignocaina, en concentraciones sanguíneas que reducen la arritmia cardiaca, reduce de forma acentuada la broncoconstricción de reflejos, pero ejerce poco efecto, relativamente, sobre la iniciada por los mediadores alérgicos.

Br. J. Anaesth. (1980), **52**, 879

EFFECT OF DROPERIDOL ON DOPAMINE-INDUCED INCREASE IN EFFECTIVE RENAL PLASMA FLOW IN DOGS

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SUMMARY

The interaction between small doses of dopamine and droperidol on effective renal plasma flow was studied in dogs. Small doses of dopamine are known to produce renal vasodilatation by a dopaminergic mechanism and droperidol, a selective dopamine antagonist used in neuroleptanaesthesia, may attenuate this response. Effective renal plasma flow was measured non-invasively using ^{125}I-hippuran. A 20-min infusion of dopamine 2 μg kg^{-1} min^{-1} significantly enhanced effective renal plasma flow (mean increase of 16%; $P < 0.05$) in anaesthetized dogs. This effect was abolished (mean decrease 6.6%) by droperidol 0.2 mg kg^{-1} administered at the commencement of anaesthesia. It is concluded that droperidol reduces the renal vasodilatation induced by dopamine in anaesthetized dogs.

The haemodynamic effects of dopamine are crucially dependent on dose (Goldberg, 1972). In low doses it has a unique action, increasing renal blood flow via an action on specific dopamine receptors (Yeh, McNay and Goldberg, 1969). Dopamine is used increasingly for the prophylaxis and treatment of cardiogenic shock following open-heart surgery (Holtzer et al., 1973; Daenen, de Leval and Stark, 1977; Hess et al., 1979).

The butyrophenone, droperidol, is frequently used in anaesthesia, including that for open-heart surgery (Whitwam and Russell, 1971) and drugs in this class are known to be selective dopamine antagonists (Anden et al., 1970). This study was undertaken to determine whether the response of the renal vasculature to a small dose of dopamine could be affected by a clinically acceptable dose of droperidol administered some hours before the dopamine.

A variety of factors affect renal blood flow other than those which were the subject of the study (Papper and Papper, 1964). In order to minimize these effects, it was considered necessary to use each subject as its own control. As this involved four separate experiments, dogs rather than humans were used in the investigation.

METHODS

Six beagle dogs (8–16 kg) were studied. Anaesthesia was induced with pentobarbitone sodium 30 mg kg^{-1} i.v., the trachea was intubated and the lungs ventilated artificially to normocarbia. Anaesthesia was maintained with 60% nitrous oxide in oxygen and incremental doses of fentanyl 25 μg i.v. as needed.

The bladder was catheterized and the dog placed prone on a warming blanket. Rectal temperature and e.c.g. were monitored throughout the experiment and arterial pressure was measured regularly using a sphygmomanometer. An isotonic solution (Compound Sodium Lactate Injection B.P.) was infused via a cannula placed in a hind limb vein and the rate adjusted to deliver 100 ml h^{-1}. Samples for blood-gas analysis and gamma counting were removed via a cannula inserted in a forelimb vein. Before measurement of effective renal plasma flow (ERPF), the bladder was completely emptied and the catheter occluded.

A gamma camera was positioned over the kidneys and 100 μCi of ^{125}I-labelled hippuran was injected via the infusion cannula. Radioactivity over the kidneys was monitored continuously and renograms plotted by a computer (Nuclear Data). These plots were used as a qualitative assessment of renal perfusion and no dog was included in the study if its renal perfusion was inadequate. A quantitative estimate of renal blood flow was started concurrently and continued if the renogram was normal. Five-millilitre blood samples were collected at 1, 5, 10, 20, 30, 45, 60, 75 and 90 min after injection of ^{125}I-hippuran. All the urine was collected at the end of the 90-min period and the volume measured. The bladder was washed repeatedly with isotonic solution until no radioactivity remained. Urine and washings were added together and made up to a standard volume. Effective renal plasma flow was calculated using the single injection method with

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007-0912/80/090879-05 $01.00

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urine collection. The advantages of this method for estimating ERPF have been reviewed by O'Reilly, Shields and Testa (1979). In each experiment two consecutive measurements of ERPF were obtained.

Each dog was assigned to one of the following plans of study on a random basis so arranged that each received the four treatments on four consecutive occasions:

(1) Twenty minutes infusion of dopamine 2 μg kg^{-1} min^{-1} beginning 5 min before a second renogram and measurement of ERPF.
(2) Control infusion of isotonic solution in equivalent volumes.
(3) Droperidol 0.2 mg kg^{-1} injected i.v. just after induction of anaesthesia followed by a 20-min infusion of dopamine as in (1).
(4) Droperidol injected as above with a control infusion as in (2).

The effects of dopamine or control infusion on ERPF were expressed as percentage change from the first ERPF measured during the same experiment. Significance of differences between treatments was calculated using a nested analysis of variance, otherwise a paired *t* test was used. Results are expressed as means ± SD.

Each dog was allowed 2–4 weeks for recovery between experiments.

The total dose of fentanyl administered did not differ significantly in the four treatments (table I).

RESULTS

Only one dog was rejected because of inadequate renal perfusion. This was demonstrated by widening of the renogram curve and slow build up of radioactivity in the bladder (fig. 1).

The addition of droperidol to the anaesthetic regimen did not significantly alter ERPF measured in this study (table I). Dopamine 2 μg kg^{-1} min^{-1} produced significantly greater ERPF than the control infusion, but this was abolished when droperidol was present (table II). (The nested analysis of variance showed that the ERPF was significantly altered by the nature of the infusion rather than by the anaesthetic used.)

Heart rate, arterial pressure and rectal temperature were not significantly different in the groups of dogs receiving anaesthesia with or without droperidol (table I). We confirmed in this study that the dose of dopamine used had no effect on the heart rate and arterial pressure. The maximum change in systolic arterial pressure which occurred during the dopamine infusion was -1.13 ± 2.08 kPa and the maximum heart rate change was -6.8 ± 5.1 beat min^{-1}. These changes were not significantly different from those measured during the control infusion.

The change in urine volume from the first and second estimation suggests that droperidol did not inhibit the effects of dopamine in this respect (table II). However, the urine output was extremely variable, sometimes only small quantities being collected over a 90-min period. All the dogs which received a standard anaesthetic and dopamine showed an increase in urine volume (range +1.0 to +192.5 ml). Two dogs in the droperidol-treated group showed a decrease in urine output (range for all six dogs −30 to 118 ml).

DISCUSSION

We have confirmed that a 20-min infusion of dopamine 2 μg kg^{-1} min^{-1} improves ERPF in the dog. Furthermore, we have demonstrated that droperidol 0.2 mg kg^{-1} abolishes this effect. There was no evidence that droperidol alone had any effect on ERPF at this dose.

Whilst it was not possible to demonstrate that droperidol significantly reduced the increase in urine volume produced by dopamine, the addition of droperidol to the anaesthetic made the response to dopamine less predictable.

TABLE I. *Initial values (mean ± SD). *Group I* v. *group II paired* t *test. n.s. = not significant*

	Group I (control)	Group II (droperidol 0.2 mg kg^{-1})	Significance*
Effective renal plasma flow (ml min^{-1})	65.3 ± 25.5	63.7 ± 30.6	n.s.
Systolic arterial pressure (kPa)	13.5 ± 2.5	12.5 ± 2.9	n.s.
Heart rate (beat min^{-1})	94.2 ± 16.6	102.3 ± 11.6	n.s.
Rectal temperature (°C)	36.5 ± 1.0	36.8 ± 0.3	n.s.
Total dose of fentanyl (μg)	102.1 ± 44.5	103.8 ± 37.6	n.s.

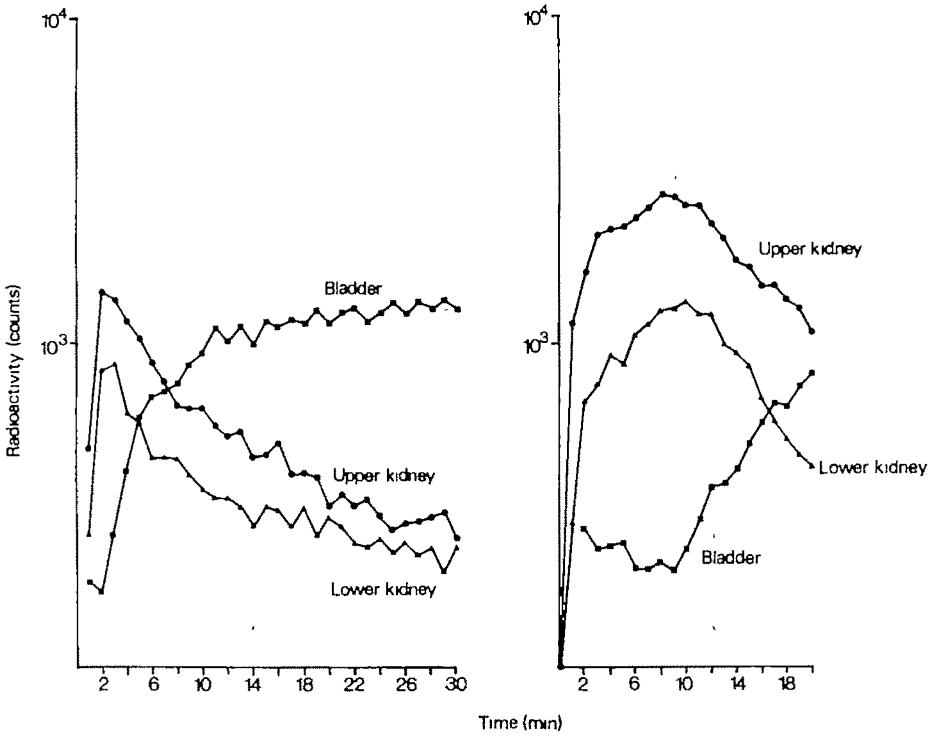

FIG. 1. Renograms obtained from anaesthetized dogs injected with ^{125}I-hippuran 100 μCi. The left-hand curves were obtained from a normal dog and the right-hand curves were obtained from a dog rejected because of inadequate renal function.

TABLE II. *Change* in effective renal plasma flow (ERPF) and urine production induced by a 20-min infusion of dopamine 2 μg kg^{-1} min^{-1} or a control infusion of isotonic solution in anaesthetized dogs with and without droperidol 0.2 mg kg^{-1}. n.s. = Not significant; d.f. = degrees of freedom. *Change was calculated from the immediately preceding measurement of ERPF or urine production where no infusions were administered (table I). †Significantly different from control infusions*

	ERDF (mean % change)	Urine volume (ml) (mean change over 90 min)
Standard anaesthetic		
Dopamine infusion	+15.98†	+44.9†
Control infusion	−12.60	+10.5
Droperidol anaesthetic		
Dopamine infusion	−6.64	+30.9†
Control infusion	−13.8	+0.03
Nested analysis of variance:		
Contribution to change in values		
from anaesthetics	$F = 0.065$ (n.s.)	$F = 0.419$ (n.s.) (1, 2 d.f.)
from infusions	$F = 4.63$ ($P < 0.05$)	$F = 3.64$ ($P < 0.05$) (2, 20 d.f.)

In man, Birch and Boyce (1977) found that droperidol did not attenuate the effect of an infusion of dopamine 20 μg kg^{-1} min^{-1}. However, as pointed out by Zimmerman (1978), this dose of dopamine was too great to produce renal vasodilatation by a specific dopaminergic mechanism. A more selective dose of dopamine was used in man and dogs by Goto, Fujita and Fuse (1979). These authors found that droperidol apparently increased the effects of dopamine on urine flow and the excretion of sodium and inorganic phosphate. The findings in the present study suggest that droperidol may attenuate the effect of dopamine on urine volume. There was no suggestion that droperidol increased urine volume. These differences may be explained by the timing of the droperidol administration. Goto, Fujita and Fuse (1979) administered droperidol at the time of the dopamine infusion in dogs. In the present study, in order to simulate clinical practice, droperidol was administered at induction of anaesthesia, a minimum of 2 h before the administration of dopamine.

The accepted clinical dose of droperidol is 0.07–0.3 mg kg^{-1} (Morgan, Lumley and Gillies, 1974). Thus, the dose of droperidol used in this study which attenuated the effects of dopamine was well within the clinical range.

Our investigation in dogs indicates that the use of small-dose dopamine infusions to increase renal blood flow may be ineffective in patients given droperidol some hours previously. A carefully controlled study in man is needed to confirm this.

ACKNOWLEDGEMENTS

The authors are grateful to Miss Stephanie E. Maddison, Ms Margaret Marple and Miss Anne Marie McNeilly for technical assistance with this project.

This study was supported in part by a grant from Arnar-Stone Laboratories. A preliminary account of part of this work was presented to the Anaesthetic Research Society, Southampton Meeting, March 1979.

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EFFET DU DROPERIDOL SUR UNE AUGMENTATION DU DEBIT EFFECTIF DE PLASMA RENAL PROVOQUEE PAR LA DOPAMINE CHEZ LES CHIENS

RESUME

On a procédé sur des chiens à une étude de l'interaction qui se produit entre petites doses de dopamine et de dropéridol sur le débit effectif de plasma rénal. Les petites doses de dopamine produisent, on le sait, une vasodilatation rénale par un mécanisme dopaminergique et le dropéridol, qui est un antagoniste sélectif de la dopamine, que l'on utilise dans le domaine de la neuroleptanesthésie, peut atténuer cette réaction. On a mesuré d'une manière non envahissante le débit effectif de plasma rénal en utilisant ^{125}I-hippuran. Une infusion de dopamine d'une durée de 20 min à raison de 2 µg kg^{-1} min^{-1} a stimulé le débit effectif de plasma rénal (augmentation moyenne de 16%) ($P<0,05$) sur des chiens anesthésiés. Cet effet a été aboli (baisse moyenne de 6,6%) à l'aide de dropéridol administré à raison de 0,2 mg kg^{-1} au commencement de l'anesthésie. On en a conclu que le dropéridol diminue la vasodilatation rénale provoquée par la dopamine sur des chiens anesthésiés.

WIRKUNG VON DROPERIDOL AUF DURCH DOPAMIN BEWIRKTEN, ERHÖHTEN NIERENPLASMADURCHFLUSS BEI HUNDEN

ZUSAMMENFASSUNG

Die Wechselwirkung zwischen kleinen Dosen von Droperidol und Dopamin auf den effektiven Nierenplasmadurchfluss wurde in Hunden untersucht. Kleine Dopamindosen bewirken bekanntlich Nierengefasserweiterung durch einen dopaminenergischen Mechanismus, und Droperidol, ein selektives Dopamin-Gegenmittel, das bei neuroleptischer Narkose verwendet wird, kann diese Reaktion verstärken. Der effektive Nierenplasmadurchfluss wurde nicht-invasiv mittels ^{125}I-Hippuran gemessen. Eine 20 Minuten dauernde Infusion von 2 µg kg^{-1} min^{-1} Dopamin verbesserte den Nierendurchfluss wesentlich (mittlerer Anstieg 16%) ($P<0,05$), bei narkotisierten Hunden. Beendet wurde diese Wirkung (mittlerer Abstieg 6,6%) durch Droperidol 0,2 mg kg^{-1}, verabreicht zu Narkosebeginn. Es wird gefolgert, dass Droperidol bei Hunden dei durch Dopamin eingeleitete Nierengefasserweiterung reduziert.

EL EFECTO DEL DROPERIDOL EN LA DOPAMINA INDUJO UN INCREMENTO DEL FLUJO EFECTIVO DEL PLASMA RENAL EN PERROS

SUMARIO

Se estudió la interacción entre pequeñas dosis de Dopamina y de Droperidol sobre el flujo efectivo del plasma renal. Se sabe que penqueñas dosis de dopamina producen dilatación de los vasos renales mediante un mecanismo dopaminérgico, y el droperidol que es una dopamina antagónica de tipo selectivo usada en neuroleptanestesia, puede atenuar esta respuesta. El flujo efectivo de plasma renal se midió de forma no invasora, usando ^{125}I-hipurán. Una infusión de 2 μg kg^{-1} min^{-1} de dopamina durante 20 minutos incrementó el flujo efectivo de plasma renal (incremento medio del 16%) ($P<0{,}05$), en perros anestesiados. Este efecto se anuló (disminución media del 6,6%), mediante el uso de 0,2 mg kg^{-1} de droperidol, administrado al principio de la anestesia. La conclusión es que el droperidol reduce la dilatación de los vasos renales, que indujo la dopamina en los perros anestesiados.

Br. J. Anaesth. (1980), **52**, 885

COMPARISON OF PERSONAL POLLUTION MONITORING TECHNIQUES FOR USE IN THE OPERATING ROOM

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SUMMARY

Three personal pollution monitors (adsorption tubes, diffusion dosimeters and evacuated bottles) have been tested, in routinely used operating rooms and under controlled laboratory conditions, for their accuracy and reproducibility relative to one another and to measurements by infra-red spectroscopy. All the techniques provide time-weighted average measurements of pollutant concentrations. Tubes and dosimeters measure halothane with greater accuracy than that required by N.I.O.S.H. regulations, but neither technique can measure inorganic pollutants such as nitrous oxide. The prototype evacuated bottles tested are unsatisfactory at their present stage of development for the measurement of both halothane and nitrous oxide concentrations. We believe that, at the present time, surveys of operating room pollution can best be carried out using adsorption tubes or diffusion dosimeters for personal halothane concentrations and a portable infra-red spectrometer for measurement of background nitrous oxide concentrations.

Because of suggestions that chronic exposure to small concentrations of waste anaesthetic gases may be associated with a health risk to operating room staff, much attention has been given to methods for determining the actual concentration of these gases and vapours in theatre air. Robinson and co-workers have criticized some of the earlier pollution studies for lack of analytical detail and for use of potentially inaccurate sampling methods such as the collection of air samples in syringes and plastic bags (Robinson et al., 1976). These methods were inaccurate because leakages and adsorption of organic vapours on to certain plastics were difficult to eliminate. A further criticism of these early studies is that the results were determined from the collection of spot samples, that is, samples in which the anaesthetic gas concentration referred only to one sampling site at one particular time. Using spot sampling methods, a comprehensive survey of the pattern of pollution can only be built up by collecting many samples over a period of time and at a number of sites. This requires a great commitment of time and effort.

More recent surveys of operating room pollution (Halliday et al., 1979; Halsey, Davenport and Wardley-Smith, 1979) have utilized integrated sampling methods. These methods provide the time-weighted average (TWA) concentrations to which individuals are exposed in their working environment. Such monitoring is carried out either at a fixed site or, more commonly, by a personal monitor worn by the staff concerned. At the present time the aim of operating room pollution monitoring is to build up a set of reliable measurements which can be used in recommending maximum permitted concentrations of anaesthetic gases to which staff may be exposed. TWA exposure values can provide such a set of data and, in the form of threshold limit values, are already the recognized means of control in industrial pollution legislation (H.M. Factory Inspectorate, 1978).

There is therefore a need to identify a reliable integrated sampling method suitable for use in operating rooms. Although several methods are now available, they have not been tested against each other, nor against other established monitoring techniques such as infra-red spectroscopy, a reliable nitrous oxide monitor which can provide TWA measurements. In addition, methods which have proved satisfactory in industrial pollution control need to be re-examined with regard to the special problems arising in the operating room environment. In the operating room, measurement of both organic and inorganic compounds is required; pollutants other than anaesthetic gases may interfere in otherwise straightforward analytical techniques; and unobtrusiveness and ease of use of a sampler is of the utmost importance to staff.

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0007-0912/80/090885-08 $01.00

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We have examined three methods of integrated sampling with regard to these special problems: sampling with adsorption tubes, with evacuated bottles and with organic vapour dosimeters. Collection of pollutants by drawing air through adsorption tubes is a standard method in industrial pollution control (Pellizzari et al., 1976; Brookes, Jickells and Nicolson, 1978) and has been applied to the problems of operating room pollution monitoring (Gelbicova-Ruzickova, Novak and Janak, 1972; Carter and Halliday, 1978; Halliday and Carter, 1978). Integrated sampling using evacuated aluminium bottles is a recent adaptation by Davenport and colleagues (1976) of a spot sampling method. Organic vapour dosimetry is a relatively new method in which pollutants are allowed to diffuse on to a charcoal collection element. This method has been successfully applied to industrial pollution problems (Tompkins and Goldsmith, 1977; Bamberger et al., 1978). The three methods were compared with each other and with infra-red spectroscopy, under controlled laboratory conditions and also under normal operating room conditions.

MATERIALS AND METHODS

Adsorption tubes

The adsorption tubes, personal and background samplers and methods of analysis have been described elsewhere (Carter and Halliday, 1978; Halliday and Carter, 1978). For the purposes of this investigation, tubes were analysed on the same day as the samples were collected. The tubes were taken from a stock of 20 tubes which had been used in the operating room over a period of 12 months. Halothane, ethanol and isopropanol concentrations were measured, but only halothane results are reported here.

Diffusion dosimeter

The organic vapour dosimeter (Gasbadge, Abcor Inc., U.S.A.) was a small light personal sampler (51 × 65 × 16 mm, 25 g) which was attached to the anaesthetist's gown. Sample collection occurred by diffusion so that no external power source was necessary. The replaceable collection element was activated charcoal fibre. Before use, an unused element was placed in the dosimeter which was then sealed to prevent unwanted contamination. The sampling period commenced when the seal was removed in the operating room and ended when it was replaced. The collection element was used once, analysed and discarded.

A desorption and analytical procedure suitable for the pollutants found in operating rooms has been described by Halliday and Anderson (1980). Briefly, the adsorbed pollutants are desorbed into carbon disulphide, aliquots of which are analysed by gas chromatography. The chromatographic conditions were such that the three main organic pollutants in operating room air—halothane, ethanol and isopropanol—were completely separated.

Evacuated bottles

The evacuated aluminium bottles were manufactured by Cassella and Co. Ltd, and apparently were prototypes. Only two bottles out of a set of six were used. Air leaks from broken seals between the inlet valve assembly and the container occurred in the other four bottles. All six bottles had been used over a period of months and the leaks appeared gradually over that time. For withdrawing samples from the bottles we used a technique similar to that given by Davenport and colleagues (1976). A 50-ml glass syringe was paired with an evacuated bottle and used only to extract samples from that bottle. The errors in measuring the volume of air required to fill the bottle to atmospheric pressure and the mixing volume of air remaining in the syringe were determined by using the bottles as spot samplers and taking samples from known mixtures simultaneously into the bottle and the gas chromatograph. The error was found to be +2.5% and +6% for the two bottles used in this study, 10 determinations being carried out for each bottle–syringe pair.

The evacuated bottles were analysed for both nitrous oxide and halothane. The chromatographic conditions for analysis of halothane in air followed those described by MacDonald and MacKenzie (1976). The system was calibrated in the range 0–25 p.p.m. (v/v) halothane using a dynamic gas mixing rig. Nitrous oxide was analysed as follows. Air samples from the bottles were introduced via a 0.1-ml gas sampling loop into the chromatograph, a Pye 104 series electron capture detector with a 2 m × 4 mm glass column packed with charcoal, 60/80 mesh. The operating conditions were: oven temperature 458 K; detector temperature 523 K; carrier gas (Air Products High Purity nitrogen) flow 100 ml min^{-1}; pulse space mode, 0.1 ms. The nitrous oxide retention time was 2 min. The chromatograph was calibrated with known concentrations of nitrous oxide in air in the range 0–300 p.p.m. prepared in the dynamic gas mixing rig. Above 300 p.p.m. the electron capture detector response became alinear. Any sample containing a greater concentration could be diluted and re-analysed on the linear part of the response curve. This was necessary for the samples collected during operating sessions 5 and 6.

Laboratory tests

The dynamic gas mixing rig used for calibration of the gas chromatographs and the infra-red spectrometer was also used in the laboratory tests to produce known concentrations of nitrous oxide and halothane. The apparatus consisted of a 10 litre min^{-1} flow of air into which could be leaked known flows of halothane or nitrous oxide. The source of halothane was a Drager halothane vaporizer at a nominal 1% halothane setting. The nitrous oxide source was a 20% mixture of nitrous oxide in air. The nominal concentrations produced by this apparatus were checked by comparison with those produced by a standard atmosphere generator. The detailed results of this comparison are to be published elsewhere (B. I. Brookes, Strathclyde Regional Chemists' Department, Glasgow), but tests showed that the mixing rig concentrations were 15% greater than those from the standard atmosphere generator. All calibration and test concentrations which depended on the gas mixing rig have therefore been corrected by this amount.

The gas mixing apparatus incorporated two glass mixing reservoirs and during test runs two evacuated bottles, one diffusion dosimeter and one adsorption tube and pump were suspended in the centre of the second reservoir. The known mixture of nitrous oxide and halothane was then connected to the reservoir inlet and maintained for a period of 2.5 h. During this period, the concentration in the reservoir was monitored at 5-min intervals by taking air samples via a nylon sampling line directly to the gas chromatograph. From the gas chromatograph measurements a graph of concentration against time was obtained. The average concentration to which the samples were exposed was calculated using the area under the graph as measured by planimetry. When nitrous oxide was being sampled the exit line from the reservoir was led through the infra-red analyser operated with the analyser pump off.

Operating room tests

The samplers were tested under routine operating room conditions over six operating sessions in the same room. The anaesthetist wore an adsorption tube, a badge dosimeter and an evacuated bottle and samples were taken from the areas of his chest below his mask. In addition, sampling of background concentrations of pollution was carried out with two adsorption tubes, a second evacuated bottle and the infra-red analyser with recorder. These background samplers were positioned on a trolley approximately 2 m behind the patient's head. A technician remained in the operating room at all times, was responsible for all zero and flow rate checks and kept a record of sampling times and unusual events in the room. The operating room had no air-conditioning or scavenging system. All the samples were analysed within 4 h of the end of the operating session.

RESULTS

All concentrations are reported as p.p.m. (ideal, v/v).

Laboratory tests

The performance of the samplers in measuring known halothane concentrations is shown in table I. The dosimeter badge and the adsorption tubes gave results which were within 0.2 p.p.m. of each other and within ±10% of the actual concentration to which they were exposed. The evacuated bottles gave consistently low results and on only two occasions were the measurements within 10% of the actual concentration.

TABLE I. *Performance of the personal samplers in measuring known concentrations of halothane. Ratio = (technique measurement)/(calibrated concentration)*

Halothane concentration						
Atmospheric	Gasbadge		Adsorp. tube		Bottle	
(p.p.m.)	p.p.m.	Ratio	p.p.m.	Ratio	p.p.m.	Ratio
3.4	3.3	0.97	3.1	0.91	2.7	0.79
5.0	5.5	1.10	—	—	—	—
5.6	6.0	1.07	6.1	1.09	4.9	0.88
					4.6	0.82
6.9	6.6	0.96	6.6	0.96	6.8	0.99
					6.4	0.92
8.1	8.0	0.99	8.1	1.0	6.5	0.80
					7.1	0.88
Mean		1.02		0.99		0.87
SD		0.06		0.07		0.07

Of the three methods, only the evacuated bottle method could measure nitrous oxide concentrations and its performance in this was compared with measurements from the Miran infra-red analyser. Before each experiment, the chromatograph and the Miran analyser were calibrated simultaneously using the same calibration mixtures. The bottle results were on average 6% and 16% greater than those of the Miran, but individual results showed a much larger variation between the two methods (table II).

TABLE II. *Performance of the evacuated bottles in measuring known concentrations of nitrous oxide. Ratio = (bottle measurement)/(infra-red measurement). Combined results give mean* 1.11, *SD* 0.17, *n* = 11

Nitrous oxide concentration				
Infrared analyser	Bottle 1		Bottle 2	
(p.p.m.)	p.p.m.	Ratio	p.p.m.	Ratio
158	175	1.11	192	1.22
170	195	1.15	217	1.28
215	239	1.11	229	1.07
222	284	1.28	296	1.33
322	314	0.98	—	—
Mean		1.06		1.17
SD		0.18		0.15

Theatre tests

A comparison between tubes, gasbadge and bottles, all used as personal samplers, was obtained from the measurement of the anaesthetist's exposure to halothane (fig. 1). The gasbadge and tube measurements were within 1.3 p.p.m. of each other, excluding session 3, and for session 3 an exceptionally high concentration of halothane was shown independently by both methods. Tube measurements were on average 87% of badge measurements, ranging from 75% to 99%. Bottle measurements were on average 53% of gasbadge measurements, ranging from 21% to 100%, and did not show the very high halothane concentration in session 3. Figure 2 shows the comparison between tubes and bottles, used as background samplers for halothane. The measurements given by the two background tube samplers were within 0.3 p.p.m. over four sessions and 0.5 p.p.m. at session 2. Background halothane concentrations were approximately one-third of personal halothane concentrations, and in this environment bottle measurements were in better agreement with those from the adsorption tubes. Excluding session 1, the results were within 1.5 p.p.m. of each other, the bottle measurements being on average 99% of the tube measurements. There was no obvious explanation for the high background measurement given by the bottle method in session 1 and this did not coincide with a high personal exposure measurement from the anaesthetist's bottle sampler.

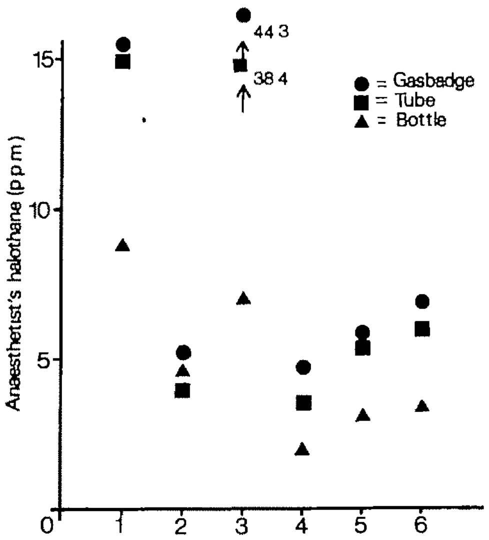

FIG. 1. Time-weighted average personal exposure of anaesthetist to halothane measured by three different methods during six operating sessions in the same operating room.

Figure 3 shows the relationship between Miran and bottle techniques used as background samplers for nitrous oxide. Both techniques show high levels of nitrous oxide pollution, but the bottle measurements were on average only 36%, ranging from 28% to 59%, of the Miran measurements. Sessions 1–4 involved the same anaesthetist, but a different anaesthetist was present in sessions 5 and 6, during which the Miran measurements showed a marked increase in background nitrous oxide concentrations which was

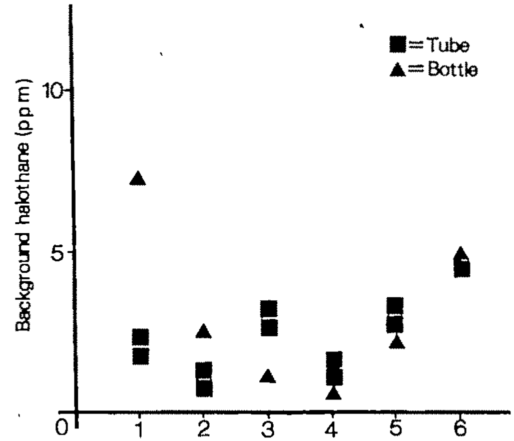

FIG. 2. Time-weighted average background concentrations of halothane in the operating room, measured by two different methods.

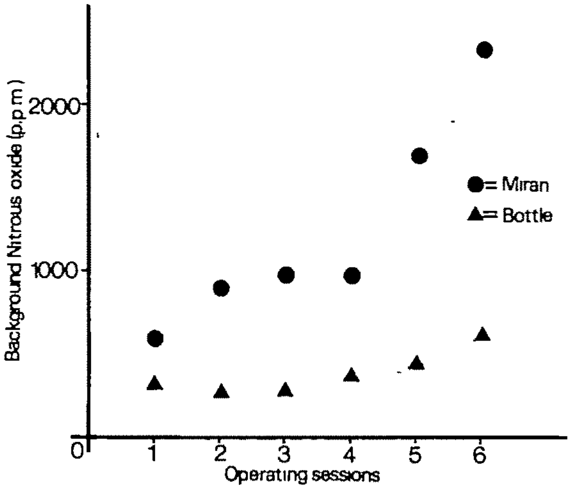

FIG. 3. Time-weighted average background concentrations of nitrous oxide in the operating room, measured by two different methods.

not accompanied by a similar increase in the bottle measurements.

The relationship between personal and background exposures as measured by tubes and bottles is summarized in table III. Both techniques measured an increased personal : background ratio for session 3.

DISCUSSION

Acceptability to staff

Adsorption tubes and evacuated bottles are used within the Eastern District of the Greater Glasgow Health Board and have proved acceptable to the anaesthetists, nurses and dentists who wear them. In the present investigation only the adsorption tube technique required an external power source, which consisted of a battery-operated low-flow air pump designed to be worn in the operating room and to cause the minimum of vibration. The dosimeter badge was used in operating rooms for the first time during this investigation and was readily accepted by staff possibly because of its resemblance to the familiar x-ray dosimeter badge.

Accuracy

The advantage of performance testing under controlled laboratory conditions is that the accuracy of the sampling method can be measured using known concentrations of pollutants. Laboratory tests showed that both the dosimeter badge and the adsorption tubes measured halothane to within ±10% of the concentrations present. This level of accuracy is similar to the performance of these techniques in industrial pollution control (Bamberger et al., 1978; Brookes, Jickells and Nicolson, 1978). The evacuated bottle measurements showed a much greater deviation from the given concentrations for both halothane and nitrous oxide.

No accuracy requirements for pollution monitors have been laid down by the British Factory Inspectorate, but the United States National Institute for Occupational Safety and Health (N.I.O.S.H.) requires that all monitoring techniques be accurate to ±25% within 95% confidence limits. Figure 4 shows the accuracy of the badge, tube and bottles expressed as the ratio of technique measurement to calibrated concentration. In order to meet N.I.O.S.H. requirements, 95% confidence limits of these ratios should be between 0.75 and 1.25. Both the badge and the adsorption tubes meet the N.I.O.S.H. requirements in their measurements of halothane concentrations and are known to do so for other organic

TABLE III. *Relationship between anaesthetist's exposure and background concentrations of halothane, as measured by the tube and the bottle samplers. Tube a and b results have been calculated using the two sets of background tube measurements. Figures in parentheses are averages which omit session* 3

Pollutant sampler	(Anaesthetist : background exposure) ratio Session 1	2	3	4	5	6	Average
Halothane							
Tube a	6.7	3.5	12.4	3.5	2.0	1.7	5.0 (3.5)
Tube b	6.5	6.5	13.2	2.6	1.9	1.3	5.3 (3.8)
Bottle	1.2	2.1	8.6	3.5	1.3	0.7	2.9 (1.8)
Nitrous oxide							
Bottle	1.1	1.9	5.2	1.8	1.0	0.9	2.0 (1.3)

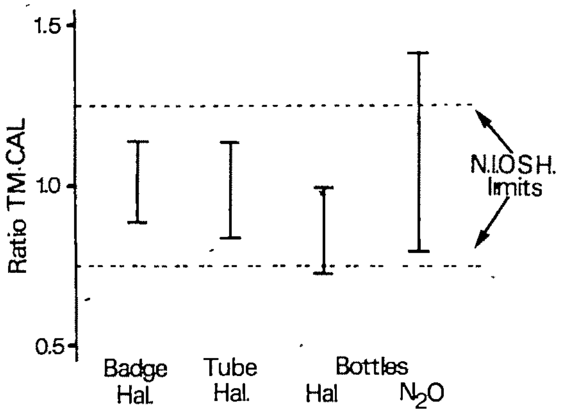

FIG. 4. Performance of the personal samplers expressed as the ratio of technique measurement (TM) to calibrated concentration (CAL). The 95% confidence limits for measurements made with the samplers are shown as vertical bars against the N.I.O.S.H. performance limits.

pollutants. The evacuated bottles as presently available do not meet this ±25% accuracy limit.

Performance in theatre

Correlations between side-by-side operating room samples are important to verify that there is general agreement between different methods of sampling. The actual concentration of pollutants in the operating room is, however, unknown and changing and can only be measured using other sampling techniques which vary in their performance. Therefore, close agreement between different sampling methods should not always be expected, but different methods should show the same patterns of response under the same conditions. The measurements of anaesthetists' personal exposure to halothane showed a large discrepancy for session 3 between the dosimeter badge and tube measurements compared with the bottle measurement and throws suspicion on the reliability of the bottle technique. Another discrepancy was found in sessions 5 and 6 when the infra-red analyser indicated large increases in background nitrous oxide concentrations which were not seen in the bottle measurements.

The evacuated bottle measurements of both halothane and nitrous oxide in the operating room were consistently less than the measurements from the other techniques. Laboratory tests with halothane also showed a low response from the bottles, although by only 13% compared with approximately 40% in operating room measurements. However, in laboratory tests using nitrous oxide the results obtained with the bottles were greater than those obtained with the other techniques. Adsorption of vapour on the interior of the bottles and on the flow control valve may explain the consistently low measurements for halothane, but this adsorption should not occur with nitrous oxide and we can offer no satisfactory explanation for the low bottle measurements of operating room nitrous oxide concentrations.

Infra-red analysis provides a reliable method for monitoring nitrous oxide concentrations. Although it cannot be used as a personal monitor, it can provide time-weighted average values at any chosen site and was recommended as a simple and reliable method in the N.I.O.S.H. survey of pollution by anaesthetic gases (Whitcher et al., 1975). The same survey warned that halothane analysis by infra-red was subject to interference from other pollutants present in operating room air and our own experience confirms this.

Suggestions for further work

Halothane and nitrous oxide are the anaesthetic waste gases most likely to be measured in an operating room pollution survey. The dosimeter badge and the adsorption tubes have shortcomings as operating room monitors because of their inability, as used in this investigation, to measure nitrous oxide. The charcoal collection element of the dosimeter badge cannot retain quantitatively the relatively great concentration of nitrous oxide in operating room air. The adsorbent material used in these adsorption tubes does not retain nitrous oxide, but if a suitable adsorbent material could be found the tube technique could be easily adapted to monitor nitrous oxide. It is possible that materials such as molecular sieves may take up nitrous oxide molecules fairly efficiently. In principle, the evacuated bottle is an attractive technique and can measure both nitrous oxide and halothane but, on the evidence from this study, does not as yet provide a reliable sampling system. Design improvement, further laboratory and field testing, including the effect of storage on measurements, should be carried out, preferably at several different laboratories. Independent assessment of the adsorption techniques would also be useful, although the results reported here justify their use as halothane monitors.

After deciding on suitable sampling methods for operating room pollution monitoring, the logistical problem of collecting and analysing samples from operating room staff still remains. All methods require trained technicians, working under the supervision of a scientist, and analytical facilities, most probably gas chromatography. The survey of operating room pollution within an N.H.S. District carried out by Halliday and co-workers (1979) required two full-time technicians working for 3 months with all the back-up facilities of an established analytical laboratory. We estimate that within that same district, continuous monitoring of consultant anaesthetists alone would produce approximately 1000 samples per week. A compromise to continuous monitoring of all staff at risk might be to institute a programme in which the exposure of each member of staff was continuously monitored for a short period, say 1 week, repeated on a 6-monthly basis. This 6-monthly check should be carried out in conjunction with supplementary programmes such as the instigation of a code of work practice for operating room staff aimed at reducing unnecessary pollution and the installation of efficient scavenging equipment in all operating rooms.

CONCLUSIONS

No sampling technique has been officially recommended for halothane; however, adsorption techniques have been evaluated and accepted by N.I.O.S.H. as suitable for measurement of trichloroethylene and of halogenated ethanes with chemical structures similar to halothane (N.I.O.S.H. Manual of Analytical Methods, 1977). The data reported here show that both the dosimeter badge and the adsorption tube techniques can provide accurate measurements of atmospheric halothane concentrations. In the absence of an improved evacuated bottle, time-weighted average operating room pollution can be accurately monitored using either of these adsorption techniques for halothane measurement and an infra-red analyser for nitrous oxide measurements.

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COMPARAISON DES TECHNIQUES DE SURVEILLANCE DE LA POLLUTION PERSONNELLE POUR USAGE DANS LES SALLES D'OPERATIONS

RESUME

On a procédé à des essais sur trois dispositifs de surveillance de la pollution personnelle (tubes d'adsorption, dosimètres de diffusion et bouteilles évacuées) dans des salles d'opérations utilisées d'une manière routinière et dans des conditions de laboratoires contrôlées, afin de déterminer leur précision et leur reproductibilité, les uns par rapport aux autres et par rapport aux mesures obtenues par la spectroscopie à rayons infrarouges. Toutes les techniques prévoient des mesures moyennes des concentrations de polluants pondérées par le temps. Les tubes et les dosimètres mesurent l'halothane avec une plus grande précision que celle exigée par les règlements du N.I.O.S.H., mais aucune de ces techniques ne peut mesurer les polluants inorganiques tels que le protoxyde d'azote. Les prototypes de bouteilles évacuées qui ont été soumis à des essais n'ont pas donné satisfaction, à leur stade actuel de développement, pour la mesure de l'halothane et des concentrations de protoxyde d'azote. Nous croyons qu'actuellement, les enquêtes sur la pollution des salles d'opérations pourraient être mieux effectuées si l'on adoptait des tubes d'adsorption ou des dosimètres de diffusion pour les concentrations personnelles d'halothane et un spectromètre portatif à rayons infrarouges pour la mesure des concentrations résiduelles de protoxyde d'azote.

VERGLEICH VON VERUNREINIGUNGS-ÜBERWACHUNGSMETHODEN ZUR ANWENDUNG IM OPERATIONSSAAL

ZUSAMMENFASSUNG

Drei Verunreinigungs-Überwachungsgeräte (Adsorptionsrohren, Diffusionsdosimeter und Vakuumflaschen) wurden in routinemässig verwendeten OP-Sälen und unter kontrollierten Laboratoriumsbedingungen getestet—auf ihre Genauigkeit und Reproduzierbarkeit im Verhältnis zu einander und zu Messungen durch Infrarot-Spektroskopie. Alle diese Methoden ergeben zeitbedingte Durchschnittsmessungen der Verunreinigungskonzentration. Rohren und Dosimeter messen Halothan mit grösserer Genauigkeit als von den N.I.O.S.H.-Bestimmungen verlangt, aber keine Methode vermag anorganische Verunreinigungsstoffe wie etwa Stickoxyd zu messen. Der getestete Vakuumflaschen-Prototyp ist im gegenwärtigen Entwicklungsstadium sowohl für die Messung von Halothan- als auch von Stickoxydkonzentrationen geeignet. Wir glauben, dass zur Zeit Untersuchungen der OP-Saal-Verunreinigung am besten durch Adsorptionsröhren oder Dosimeter durchgefuhrt werden können, was Halothankonzentrationen betrifft, und durch ein Transportables Infrarotspektrometer fur die Messung von Stickoxydkonzentrationen.

COMPARACION DE LAS TECNICAS DE VIGILANCIA DE POLUCION PERSONAL A USAR EN EL TEATRO DE OPERACIONES

SUMARIO

Se han comprobado tres monitores de polución personal (tubos de absorción, dosímetros de difusión y botellas de evacuación), en teatros de operaciones de uso rutinario y bajo condiciones controladas de tipo laboratorio, en lo que respecta a su precisión y su mútua reproductibilidad relativa, así como a lo relacionado a las mediciones mediante espectroscopía por infrarrojos. Todas las técnicas proveyeron mediciones de promedios sopesados con respecto al tiempo de las concentraciones de los polucionantes. Los tubos y dosímetros miden el halotano con una mayor precisión que la que exiguen las normas de N.I.O.S.H., pero ninguna de las técnicas puede medir los polucionantes inorgánicos tales como el óxido nitroso. El prototipo de botellas de evacuación que se verificó fue insatisfactorio en su estado actual de desarrollo, tanto para la medición de las concentraciones de halotano como de las de óxido nitroso. Creemos que en estos momentos las investigaciones de polución en los teatros de operaciones puede llevarse a cabo de forma más eficiente usando tubos de absorción o dosímetros de difusión, para las concentraciones personales de halotano, y un espectrómetro portátil de infrarrojos para la medición de las concentraciones de óxido nitroso de fondo.

Br. J. Anaesth. (1980), **52**, 893

PHARMACOKINETICS OF TUBOCURARINE ADMINISTERED BY COMBINED I.V. BOLUS AND INFUSION

M. I. RAMZAN, C. A. SHANKS AND E. J. TRIGGS

SUMMARY

Pharmacokinetic data were used to calculate an i.v. bolus dose and infusion regimen for tubocurarine (dtc). This produced continuous paralysis in 12 anaesthetized patients. In nine of the patients the duration of infusion was sufficient to achieve a "steady-state" dtc concentration in the plasma (mean 1.09 μg ml^{-1}). At the completion of the infusion, twitch response had been abolished in half of the group, but 30 min later all had a measurable response. All plasma concentrations decreased rapidly after infusion, from a mean of 1.35 μg ml^{-1}, in either a mono- or a bi-exponential manner. In all instances, a two-compartment open model was used to describe the plasma concentration–time data. The pharmacokinetic parameters derived from this study did not differ significantly from those reported for a single dose except that the plasma clearance was less.

Sustained muscular relaxation has been produced by continuous administration of tubocurarine (dtc) based on the rate of disappearance and accumulation of the drug in anaesthetized man (Ryan, 1964). The degree of relaxation was judged clinically, and from mathematical interpretation of the dtc requirements Ryan derived an equation for the exponential disappearance of dtc from the plasma and interstitial fluid.

Horowitz and Spector (1973) developed a highly sensitive radioimmunoassay for dtc and used it to obtain more precise serum dtc–time relationships in man. Matteo, Spector and Horowitz (1974), using the same assay procedure, carried out a study involving the measurement of both the serum concentration of dtc and the intensity of neuromuscular blockade in man. They reported a highly significant linear correlation between the serum concentration of dtc and the evoked twitch tension. Wingard and Cook (1976) reviewed the data obtained from the five patients of Horowitz and Spector (1973) and described the pharmacokinetics of dtc following a single i.v. dose in terms of a tri-exponential equation.

On the assumption that a constant plasma concentration of a muscle relaxant would produce a constant degree of neuromuscular block, Somogyi, Shanks and Triggs (1978) devised a dose regimen for pancuronium. Their drug dose regimen, which consisted of an i.v. bolus dose and an infusion, was calculated from the plasma clearance and the apparent volume of distribution obtained previously (Somogyi, Shanks and Triggs, 1976).

The present study also used averaged pharmacokinetic data in an attempt to design a method which might be suitable for producing continuous paralysis in the anaesthetized patient and to use these data to re-examine the pharmacokinetics of tubocurarine in man.

PATIENTS AND METHODS

Patients

Twelve adult patients (table I) without renal or hepatic disease were studied during elective surgery. All were free of known or suspected neuromuscular disease and none was receiving drugs known to affect neuromuscular transmission.

The patients were premedicated with a combination of a narcotic analgesic and atropine or hyoscine about 1 h before the commencement of anaesthesia. Anaesthesia was induced with droperidol 5–10 mg, phenoperidine 0.5 mg and thiopentone 100–200 mg i.v. Tracheal intubation was facilitated by topical analgesia of the larynx with 4% lignocaine. Further increments of thiopentone or phenoperidine were administered as required to maintain nitrous oxide–barbiturate–narcotic anaesthesia. The lungs were ventilated artificially with a mixture of nitrous oxide and oxygen to maintain an end-tidal carbon dioxide concentration of 5.0%. Core and limb temperatures were maintained by conservation of body heat.

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0007-0912/80/090893-07 $01.00

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TABLE I. *Clinical details of patients. BSA = body surface area*

Patient	Sex	Age (yr)	Weight (kg)	BSA (m^2)	Surgery	Duration of infusion (min)	Dtc (total dose) (mg)
1	M	52	76	1.92	Aorto bi-femoral anastomosis	182	76.58
2	F	34	71.3	1.71	Splenectomy	54	50.61
3	M	39	60	1.68	Exploration of pancreatic duct	123	55.14
4	M	61	61	1.68	Aorto–femoral anastomosis	110	52.80
5	M	69	73	1.94	Aorto–iliac anastomosis	270	109.94
6	F	31	57	1.57	Cholecystectomy	83	44.94
7	M	62	89	2.03	Aorto–femoral anastomosis	110	78.70
8	F	72	55	1.51	Gastrectomy	131	51.22
9	F	53	69.3	1.86	Splenectomy	62	51.02
10	F	33	68	1.77	Exploration haematoma liver	75	51.40
11	F	31	83	1.97	Hemithyroidectomy	70	61.22
12	F	17	40	1.32	Dwyer's procedure for scoliosis	140	38.80

Neuromuscular response

The forearm and hand of each patient were immobilized and a force-displacement transducer attached at right-angles to the thumb. The ulnar nerve was stimulated supramaximally at the elbow using a square wave of 0.2 ms duration every 10 s. After ensuring that the cathode was distal, the resulting mechanical twitch response was recorded. Tubocurarine was administered not less than 20 min later after a stable control twitch height had been recorded. In most cases the compound electromyogram from the hypothenar muscles was monitored.

Calculation of the dose of dtc

The pharmacokinetic basis for a combined bolus and infusion dose was that of Mitenko and Ogilvie (1972):

$$\text{Bolus dose } (B) = Vd^{\beta}.C^{ss} \quad (1)$$

and

$$\text{Infusion rate } (I) = Cl_P.C^{ss} \quad (2)$$

where Vd^{β} represents the apparent volume of distribution of the drug, Cl_P the plasma clearance and C^{ss} the desired steady-state drug concentration in plasma. The model independent parameters, the apparent volume of distribution Vd^{β} and plasma clearance Cl_P, were those obtained following a single i.v. injection of dtc (Ramzan, Shanks and Triggs, 1978). The desired steady-state drug concentration C^{ss} selected was 0.7 μg ml^{-1} (Matteo, Spector and Horowitz, 1974).

This resulted in an i.v. bolus dose of dtc of 540 μg kg^{-1} and a constant infusion rate of 2.9 μg kg^{-1} min^{-1}. After an i.v. infusion of normal saline had been established, dtc was administered into the infusion line. Dtc infusion was commenced at the time of the bolus injection and the rate of infusion was regulated by a constant rate infusion pump (Volumetric Infusion Pump, McGaw).

Blood sample collection and analysis

Blood samples were obtained from a catheter used to measure central venous pressure. These were taken just before dtc administration (blank), then at 5, 10, 15, 20, 30, 45 and 60 min and thereafter every 20–30 min during the infusion. When the infusion was terminated, the sampling routine was the same as that during the infusion with additional samples being taken at 1.5, 2, 3, 4, and where possible at 6 and 8 h after infusion. Immediately after collection, the samples were centrifuged so that the plasma could be frozen and stored until assay.

Analysis of dtc in plasma was by a fluorescence method based on the colorimetric methyl orange procedure for basic organic compounds (Brodie and Udenfriend, 1945). Glazko, Dill and Fransway (1962) reported that sensitivity of methyl orange procedures could be increased several hundred-fold by substituting fluorescent sulphonated dyes such as Xylene Red B.

Determination of dtc in this study did not require extraction of the drug from the plasma. One millilitre of plasma was added to phosphate buffer 1 ml (pH 7.8) and Xylene Red B solution 1 ml (2 mg ml^{-1} in K_2HPO_4 0.45 mol $litre^{-1}$) and mixed on a vortex mixer for 30 s to form the dye–dtc complex. Following addition of chloroform 5 ml, the dye–drug complex was extracted into the organic phase on a rotary mixer for 30 min. After centrifugation and vacuum aspiration of the upper (aqueous) layer, the fluorescence of the chloroform phase was determined using a Perkin–Elmer model 204 spectrofluorimeter (λ exciter = 550 nm; λ analyser = 560 nm).

The concentrations of dtc were calculated from a known standard curve relating dtc concentration to fluorescence intensity (dtc range in plasma, 0.1–5.0 μg ml^{-1}). Using 1 ml of plasma the method was accurate to 0.1 μg, but lesser concentrations could be measured by using a larger volume of plasma.

Pharmacokinetic analysis

Pharmacokinetic analysis of the data obtained from a combined i.v. bolus and infusion study with a neuromuscular blocking agent has been described previously (Somogyi, Shanks and Triggs, 1978). Ramzan, Shanks and Triggs (1978) indicated that the distribution of dtc in man may be adequately described by a two-compartment open model. Therefore in this study appropriate equations were fitted to each patient's plasma concentration–time data by an iterative least-squares nonlinear regression program FUNFIT (Pederson, 1977) using a CDC CYBER 72 computer system. α, β and the apparent volume of distribution of the central compartment (V_C) were obtained directly from the computer fit while the plasma clearance (Cl_P) was calculated using the relationship $Cl_P = \alpha\beta \cdot V_C/k_{21}$. The apparent volume of distribution Vd^{β} was calculated from Cl_P and β ($Vd^{\beta} = Cl_P/\beta$).

Statistical differences between the pharmacokinetic parameters from the single i.v. bolus study and the present study were analysed using an unpaired *t* test (Goldstein, 1967).

RESULTS

Five minutes following the administration of bolus dtc and the start of the infusion, the neuromuscular twitch responses were 1–22% of the control value. By 10 min the responses had decreased to less than 10% in all patients and this intensity of paralysis was maintained throughout the infusion in all but one patient. The twitch response was abolished completely in eight of the 12 patients at some time during dtc administration and in six patients the response was still absent at the end of the infusion (range 0–38% of control twitch height). Thirty minutes following the cessation of the infusion, all patients had a measurable response with the average response being 19% control (table II). The majority of the patients received atropine and neostigmine at this time and antagonism of the block was accomplished without difficulty in all cases. In four patients prolonged surgery allowed measurements to be made during 20–80% recovery interval and the mean rate of recovery from paralysis was 1.2% per min.

TABLE II. *Mean values (± SEM) for the intensities of neuromuscular blockade and the associated plasma concentrations of dtc in 12 patients*

Time (min)	Twitch response (% of control)	Mean plasma concentrations (μg ml^{-1})
During infusion		
5	9 (2)	3.23 (0.25)
10	3 (1)	2.58 (0.24)
15	2 (1)	2.30 (0.24)
20	2 (1)	2.06 (0.22)
30	2 (1)	1.80 (0 20)
45	2 (1)	1.49 (0.18)
60	4 (2)	1.43 (0.17)
2nd hour	6 (4)	1.34 (0.17)
End of infusion	6 (3)	1.35 (0.17)
After infusion		
5	7 (4)	1.07 (0.08)
10	9 (4)	0.93 (0.07)
15	12 (5)	0.86 (0.07)
20	14 (6)	0.80 (0.07)
30	19 (6)	0.72 (0.06)
45	35 (7)	0.66 (0.05)
60	—	0.59 (0.04)
90	—	0.52 (0.05)
120	—	0.43 (0.05)
240	—	0.27 (0.05)

The plasma concentration of dtc and the associated evoked neuromuscular response are shown in table II and figure 1. It was found that the maintenance of an adequate level of neuromuscular paralysis was associated with a plateau in the dtc plasma concentration. The mean plasma concentration of dtc in the 12 patients at the end of the infusion was 1.35 μg ml^{-1}. However, in three patients the requirements of surgery curtailed the infusion study and a steady state was not achieved. Their plasma concentrations at the end of the infusion were therefore much greater than the expected steady-state concentrations. In patients in whom steady state had been achieved, the mean plateau concentration of dtc was 1.09 μg ml^{-1}. Five per cent twitch height was associated with a mean plasma concentration of dtc just in excess of 1 μg ml^{-1}.

Some of the pharmacokinetic parameters derived from the patients in this study are presented in table III, with those derived from an earlier study following a single i.v. injection of dtc (Ramzan, Shanks and Triggs, 1978). When the clearance was calculated by

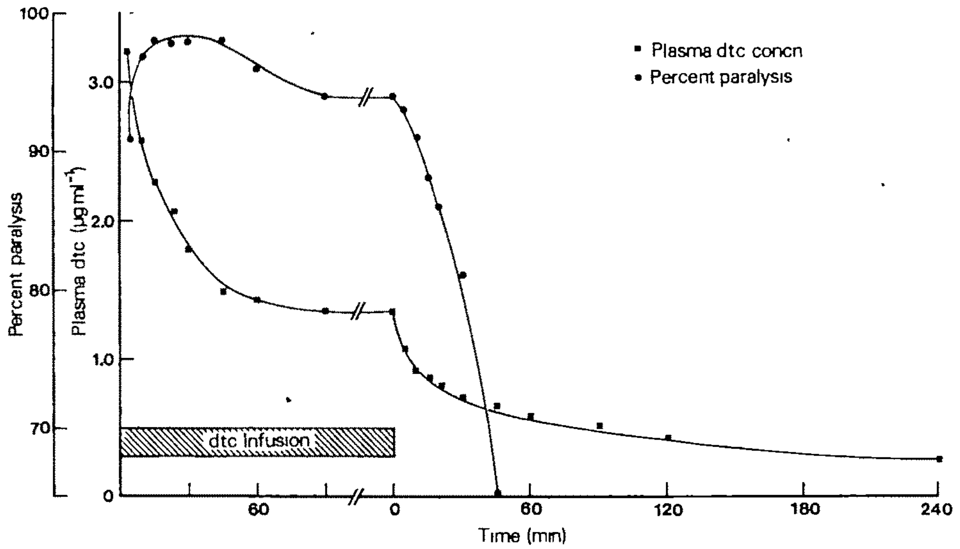

FIG. 1. Comparison of the mean plasma concentrations of dtc and the associated twitch responses following a combined i.v. bolus and infusion regimen (see table II). Following the infusion the plasma concentrations usually decreased bi-exponentially (see table IV). Percent paralysis is control twitch height – actual twitch height × 100. The line connecting these mean values is drawn visually.

TABLE III. *A comparison of the mean values (± SEM) of some of the pharmacokinetic parameters derived from the bolus/infusion study using a two-compartment open model with those obtained from a previous study (with a single bolus dose). *From Ramzan, Shanks and Triggs (1978). †Significant difference* (P < 0.01) *using an unpaired* t *test*

	Bolus/infusion	Single bolus*
Hybrid rate constant (min^{-1})		
α	0.0595 (0.0081)	0.0838 (0.0153)
β	0.0049 (0.0007)	0.0059 (0.0005)
Apparent volume of distribution ($ml\,kg^{-1}$)		
V_C	158.5 (16.3)	172.1 (26.9)
Vd_β	601.9 (70.1)	693.7 (85.3)
Plasma clearance ($ml\,kg^{-1}\,min^{-1}$)		
Cl_P	2.69 (0.29)	3.89 (0.02)†
Elimination half-life (min)		
$T_{\frac{1}{2}}\beta$	171.5 (23.0)	121.4 (10.5)
Number of patients	12	7

an alternate method (total dose administered divided by the area under the plasma concentration–time curve as measured using the trapezoidal rule extrapolated to infinite time), no significant differences were noted between the two methods. The plasma clearance calculated from this study was significantly less (unpaired *t* test) than that in the single i.v. bolus study.

The two-compartment characteristics of dtc distribution in man were examined by means of the ratios shown in table IV. The ratio β/α is used to describe

TABLE IV. *Ratios used to describe the curvature of plasma concentrations of dtc following cessation of infusion* (β/α) *as well as to describe the two-compartment characteristics of dtc* (β/k_{10}). *The smaller the ratios* β/α *the more the plasma concentration decreases in a mono-exponential manner after infusion to a steady state. Most two-compartment open model drugs have a ratio* β/k_{10} *of between* 0.2 *and* 0.6. (k_{10} *= first-order elimination rate constant.*) **Data from Ramzan, Shanks and Triggs* (1978)

Patient	β/α	β/k_{10}
1	0.07	0.40
2	0.09	0.24
3	0.07	0.26
4	0.10	0.32
5	0.09	0.23
6	0.11	0.34
7	0.05	0.23
8	0.10	0.51
9	0.08	0.16
10	0.09	0.20
11	0.10	0.29
12	0.05	0.18
Single dose study (n = 7)*		
Range	0.05–0.14	0.15–0.55

the curvature of plasma concentration following cessation of infusion, while β/k_{10} is used to describe the two-compartment characteristics of a drug as was shown for pancuronium (Somogyi, Shanks and Triggs, 1978). The range for the ratio β/α was 0.05–0.11 and did not differ significantly from the ratios obtained previously from the single i.v. bolus study (range 0.05–0.14). The range of values for the ratio β/k_{10} was between 0.16 and 0.51. Most two-compartment drugs have a ratio β/k_{10} of between 0.2 and 0.6.

DISCUSSION

The administration of dtc by combined bolus and infusion produced a "steady-state" plasma concentration of the relaxant after about 1 h in nine of the 12 patients. The mean plateau concentration of dtc in the nine patients was just in excess of 1 μg ml^{-1} and this concentration was associated with 95% neuromuscular paralysis.

Cohen, Paulson and Elert (1957) observed a close correlation between plasma concentrations of dtc and reduction of vital capacity, but found considerable variation in the activity of the individual muscle groups. Matteo, Spector and Horowitz (1974) reported a highly significant linear correlation between serum dtc concentration and the twitch tension, with recovery of twitch tension occurring at an estimated dtc concentration of 0.7 μg ml^{-1}. Miller and others (1977) reported that the plasma concentration of dtc required to depress twitch tension was similar either in patients with or those without renal failure. Their regression lines indicate that a plasma dtc concentration of 0.7 μg ml^{-1} produced approximately 80% neuromuscular paralysis. Our results suggest that the plasma concentration of dtc at the first recovery of twitch response is greater than 0.7 μg ml^{-1}. Recently, Ham and colleagues (1978) have found in the cat that the serum concentration of dtc required to produce a similar degree of neuromuscular paralysis is in excess of 1 μg ml^{-1}.

The bolus dose of dtc used in this study varied between 22 and 49 mg. The loading dose required to attain a plateau may be calculated by two methods (Gibaldi and Perrier, 1975). Using the apparent volume of distribution of the central compartment (V_C), the plasma concentration will decrease to less than the desired concentration, before the steady-state concentration is achieved. In the second method (see equations (1) and (2)) the initial concentration of drug in the plasma will be greater than the desired steady-state value, but will decrease with time to C^{ss}. Choice of the latter method was permitted by the known high therapeutic index of neuromuscular blocking agents.

The continuous infusion in our study was 2.9 μg kg^{-1} min^{-1}; this is just in excess of 12 mg h^{-1} for a 70-kg patient. Ryan (1964) reported that an infusion of dtc 15 mg h^{-1} for the first 2 h had to be reduced later to 10 mg h^{-1}. Miller and others (1974) studied 30 patients to whom an i.v. infusion of dtc was administered continuously and varied to produce constant (90%) twitch depression. They found that the infusion rate did not vary greatly, with a range of 0.143–0.255 mg per 70 kg per min (that is 8.6–15.3 mg h^{-1}). However, Miller and Eger (1976) reported that five patients required an average of only 2.1 mg m^{-2} for the period between 50 and 80 min of dtc infusion, which is about 7.4 mg h^{-1}.

The distribution kinetics of dtc have been described in terms of multi-compartment open models (Gibaldi, Levy and Hayton, 1972; Wingard and Cook, 1976; Miller et al; 1977; Buzello and Agoston, 1978a, b). Each of these workers either described the kinetics in terms of a specific three-compartment open model or fitted a tri-exponential equation to the dtc plasma concentration time data. However, we found that a two-compartment open model was able to characterize adequately the plasma concentration–time relationship of dtc in man (Ramzan, Shanks and Triggs, 1978). Similarly, the results of the present study could be interpreted in terms of a two-compartment open model.

Some of the important pharmacokinetic parameters derived from the bolus/infusion study are compared with those obtained following a single i.v. dtc study, in table III. All the parameters are in reasonable agreement with those obtained previously except that the plasma clearance was significantly less in the present study. The reduced plasma clearance (Cl_P) in this study resulted in a greater (1.09 μg ml^{-1}) steady-state dtc concentration than the anticipated value of 0.7 μg ml^{-1} but, fortuitously, this concentration of dtc was more appropriate in maintaining paralysis at a level of about 5% of control.

Estimates of the half-life of the terminal phase of the dtc plasma concentration–time curve have varied from 52 min (Smith, 1976) to 462 min (Buzello and Agoston, 1978a), but in few studies was the plasma sampling continued beyond 3 h. Horowitz and Spector (1973) had measured the concentration of dtc at 6 and 24 h on their biphasic decay curve. Wingard and Cook (1976) re-examined their data and obtained a better fit to a three-exponential equation.

The half-life of their third (slowest) phase was 150 min. However, Miller and others (1977) reported that their data were better fitted to the model of Gibaldi, Levy and Hayton (1972) than that of Wingard and Cook (1976). Miller's group suggested a half-life of 231 min. The mean half-life in our present study was 171 min. This is not significantly different from the $T_{\frac{1}{2}}^{\beta}$ found in our single dose study.

The plasma clearance (Cl_{P}) is defined as the volume of plasma from which drug is completely removed in unit time, and is a function of both the elimination half-life ($T_{\frac{1}{2}}^{\beta}$) and drug distribution. Thus:

$$Cl_{P} = 0.693\,Vd^{\beta}/T_{\frac{1}{2}}^{\beta} \tag{3}$$

A change in the clearance term is therefore a reflection of a change in either the distributional characteristics or the elimination half-life of the drug. Although Cl_{P} was significantly less in this study as compared with the single i.v. bolus study (Ramzan, Shanks and Triggs, 1978), in table III statistical differences comparing either Vd^{β} or $T_{\frac{1}{2}}^{\beta}$ did not reach significance. This lack of significance is likely to be a reflection of the wide range observed in this study for both Vd^{β} (321.9–1198.7 ml kg^{-1}) and $T_{\frac{1}{2}}^{\beta}$ (74.4–352.7 min).

In conclusion, the bolus and infusion technique for the administration of dtc offers a guide to maintenance of paralysis during prolonged surgery. The results of our regime are in good agreement with those of Ryan (1964), but the work of Miller and Eger (1976) suggests that it could produce an overdose in American subjects. However, compared with our study, Miller and Eger used the faster stimulation frequency of 0.3 Hz, a factor known to reduce the dose–response relationship (Savarese, Ali and Antonio, 1977). As our calculations are based on average data in normal subjects, disease states which alter the plasma clearance of dtc will alter the plasma concentration achieved. Assessment of neuromuscular transmission enables suitable adjustment for the individual patient and for cessation of the infusion of relaxant. With recovery of the twitch height to 5% of its control value, the dose of neostigmine needed to antagonize neuromuscular block was not dependent on the dose of relaxant administered (Miller, Larson and Way, 1972).

We calculated that a dose regimen for dtc with a bolus dose of 540 μg kg^{-1} and an infusion rate of 2.0 μg kg^{-1} min^{-1} should produce continuous paralysis in the average patient. When this regimen was tested in 12 patients for infusion durations of 62–270 min, at the end of the infusion the mean twitch response was depressed to 6% of its control height.

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PHARMACOCINETIQUE DE LA TUBOCURARINE ADMINISTREE PAR UNE COMBINAISON DE BOL INTRAVEINEUX ET D'INFUSION

RESUME

Des données de pharmacocinétique ont été utilisées pour calculer la dose du bol intraveineux et le régime d'infusion pour la tubocurarine (dtc). Celle-ci a produit une paralysie continue sur 12 patients anesthésiés. Sur neuf de ces patients, la durée de l'infusion a été suffisante pour obtenir un équilibre cinétique de la concentration de dtc dans le plasma (moyenne 1,09 μg ml^{-1}). A la fin de l'infusion, la réponse à la crispation avait disparu sur la moitié du groupe, mais 30 min plus tard tous avaient une réaction mesurable. Après l'infusion, toutes les concentrations qui se trouvaient dans le plasma ont diminué rapidement, à partir d'une moyenne de 1,35 μg ml^{-1}, soit d'une manière monoexponentielle, soit d'une manière biexponentielle. Dans tous les cas, on a utilisé un modèle ouvert à deux compartiments pour décrire les données "concentration–temps" du plasma. Les paramètres de pharmacocinétique dérivés de cette étude ne diffèrent pas beaucoup de ceux signalés pour une seule dose, sauf que le coefficient d'épuration plasmatique a été moins important.

PHARMAKOKINESE VON TUBOCURARIN, VERABREICHT KOMBINIERT ALS INTRAVENÖSER BOLUS UND ALS INFUSION

ZUSAMMENFASSUNG

Pharmakokinetische Daten wurden zur Berechnung einer intravenösen Bolus-Dosis und einer Infusionsbehandlung mit Tubocurarin (dtc) verwendet. Dies bewirkte bei 12 narkotisierten Patienten kontinuierliche Paralyse. Bei neun der Patienten war die Infusionsdauer ausreichend, eine "unveränderliche" dtc-Konzentration im Plasma zu bewirken (durchschnittlich 1,09 μg ml^{-1}). Nach Beendigung der Infusion gab es bei der Hälfte der Gruppe keine Zuckreaktion mehr, aber 30 min später zeigten alle eine messbare Reaktion. Nach der Infusion sanken alle Plasmakonzentrationen rapide ab—von einem Mittelwert von 1,35 μg ml^{-1}—einfach oder biexponentiell. In jedem Falle wurde ein offenes Modell mit zwei Kammern verwendet, um die Plasmakonzentrationszeiten zu beschreiben. Die erzielten Werte in dieser Studie unterschieden sich nicht wesentlich von denen für eine Einzeldosis—nur die Plasmaklärung war geringer.

FARMACOCINETICAS DE LA TUBOCURARINA ADMINISTRADA MEDIANTE UNA COMBINACION DE INFUSION Y DE BOLUS INTRAVENOSO

SUMARIO

Se usaron los datos farmacocinéticos para calcular un régimen de infusión y una dosis de bolus intravenoso para la tubocuranina (dtc). Este producto produjo parálisis continua en 12 pacientes anestesiados. En 9 de los pacientes la duración de la infusión fue suficiente como para lograr una concentración dtc de "estado de régimen" en el plasma (media de 1,09 μg ml^{-1}). Al finalizar la infusión, la respuesta de arrastre había desaparecido en la mitad del grupo, pero 30 minutos después todos ellos presentaron una respuesta medible. Todas las concentraciones de plasma disminuyeron rápidamente después de la infusión, a partir de una media de 1,35 μg ml^{-1}, de forma biexponencial o monoexponencial. En todos los casos se usó un modelo abierto de dos compartimientos para presentar los datos de la concentración de plasma con respecto al tiempo. Los parámetros farmacocinéticos derivados de este estudio no se diferenciaron de forma significativa de los obtenidos, y ya presentados, en el caso de dosis única, exceptuando que el espacio libre en el plasma fue menor.

Br. J. Anaesth. (1980), **52**, 901

RESPIRATORY AND PSYCHOLOGICAL EFFECTS OF ORAL TEMAZEPAM IN VOLUNTEERS

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SUMMARY

In a double-blind comparison with placebo the time-course of the effects of temazepam 40 mg and 20 mg on breathing, arterial pressure, oral temperature, cognitive function, psychomotor performance and subjective observations have been examined in 12 healthy volunteers. Temazepam 40 mg caused significant displacement of the ventilatory response to carbon dioxide 1 h after administration and a decrease in oral temperature 2 h after administration. Deficits in cognitive function were still apparent 1.5 and 2.5 h after administration and psychomotor performance did not equal control at 3.5 h. However, most subjects felt normal 2.5–3 h afterwards. Temazepam 20 mg had significant effects on cognitive function and psychomotor performance only during the 1st hour after administration.

Temazepam is a hypnotic benzodiazepine with a short half-life and a relative lack of residual or "hang over" effects (Lader, 1979). These properties could make it useful as night sedation or as anaesthetic premedication where long-term residual effects complicate subsequent drug dosage and delay recovery.

Some benzodiazepines depress respiration, for example diazepam (Utting and Pleuvry, 1975) and nitrazepam (Rudolf et al., 1978), whilst others such as lorazepam (Dodson et al., 1976) appear to have no effect. If temazepam were also without effect on breathing this would be an obvious advantage for patients with respiratory disease or who are to receive other respiratory depressant drugs.

We have investigated the respiratory effects of temazepam in volunteers and have assessed the duration of any impairment in cognitive and psychomotor function.

SUBJECTS AND METHODS

Twelve healthy volunteers were studied (table I). Except for oral contraceptives, none was taking medication during the trial; one smoker was asked not to smoke on the morning of study and all subjects were asked not to drink alcohol on the previous evening and the day of study. All tests were carried out in the morning, at least 2 h after a light breakfast, and at least 1 week elapsed between successive tests.

Before administration of any drugs control values were obtained in a number of tests.

Systolic and diastolic arterial pressure were measured using a mercury column sphygmomanometer. The same arm was used for all readings and the same observer made all the measurements. Heart rate was measured by counting the radial pulse.

A bell closed-circuit spirometer (Morgan), filled with air, was used to measure minute and tidal volume and respiratory frequency. Gases were sampled at the mouth-piece and measured continuously with an infra-red carbon dioxide analyser (Morgan) before being returned to the circuit. The carbon dioxide analyser was connected to a Rikadenki single-channel pen recorder; end-tidal $P\mathrm{CO}_2$ was calculated from the trace.

The ventilatory response to carbon dioxide was measured using the same apparatus. The soda-lime cannister was removed from the circuit and the bell of the spirometer was filled with 5% carbon dioxide in oxygen. Following a maximal expiration, the subject was connected to the spirometer and after an initial deep inspiration, was allowed to breathe quietly into the spirometer. Rebreathing took place for not more than 5 min. Minute volume was plotted against end-tidal $P\mathrm{CO}_2$; after the 1st minute the plot was linear. The best straight line was calculated by the method of least squares and the slope of the line and the $P\mathrm{CO}_2$ corresponding to 30 litre minute volume were recorded.

Cognitive function was assessed using digit symbol substitution (Wechsler, 1944) and deletion of the letter *e* from a column of newsprint. The former test

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0007-0912/80/090901-06 $01.00

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TABLE I. *Details of volunteers in the study*

Subject	Age (yr)	Sex	Weight (kg)	Smoking	Alcohol consumption	Other drugs
1	26	F	62.5	10/day	Occasional	Oral contraceptives
2	46	F	56	Nil	Occasional	None
3	30	M	75	Nil	Rarely	None
4	37	F	64	Nil	Moderate	Oral contraceptives
5	39	M	75	Nil	Occasional	None
6	27	M	65	Nil	Never	None
7	27	M	80	Nil	Never	None
8	27	M	80	Nil	Occasional	None
9	25	F	46	Nil	Rarely	None
10	36	M	80	Nil	Moderate	None
11	35	F	60	Nil	Moderate	None
12	28	F	48	Nil	Occasional	None

was carried out over 90 s and the latter over 60 s. Psychomotor effects were assessed using a pursuit rotor, which consisted of a rotating target moving at 15, 30, 40, 60 or 80 rev min^{-1}. Contact with the target was made electrically using a hinged stylus and the contact time with the target over a 60-s period was measured at each of the above speeds. Each subject was allowed one practice at this test before pre-drug values were recorded.

Identical soft gelatin capsules containing placebo, temazepam 20 mg or temazepam 40 mg were taken by the subjects on a double-blind basis; each subject received all three treatments in three experimental sessions.

After administration of the capsules, digit substitution, deletion of *e* and pursuit rotor performance were assessed at 0.5, 1.5, 2.5, 3.5 and 5 h. Arterial pressure was measured and respiratory tests repeated at 1, 2 and 3 h.

Once the first few subjects had received all three treatments, it became clear that memory deficits and a feeling of cold were common occurrences. Subsequently oral temperature was measured hourly. The subjects were asked to draw three simple symbols during the trial period and their recall of these was assessed after 6 h.

Any subjective comments were noted throughout the trial.

Statistical significance was assessed using analysis of variance and difference between means with Duncan's test.

RESULTS

The subjective effects of both doses of temazepam were apparent 15–20 min after administration of the capsule (table II). The drowsiness and feeling of cold continued for 1–2 h in most subjects and most felt normal 3 h after administration.

TABLE II. *Comments and observations. Number of volunteers exhibiting effects*

	Temazepam 40 mg	Temazepam 20 mg	Placebo
Headache	1	0	4
Ataxia	7	3	0
Drowsiness	8	7	1
Inco-ordination	3	1	0
Yawning	5	5	5
Visual problems	7	0	0
Hunger	1	1	6
Cold	7	5	2
Disorientation	1	2	0
Slurred speech	4	2	0
Sleeping	7	4	0

No significant changes were found in heart rate, arterial pressure and respiratory measurements breathing air. The ventilatory response to carbon dioxide was displaced significantly to the right by temazepam 40 mg 1 h after administration. In addition, temazepam 20 mg displaced the relationship, but this was not significantly different from control (table III). The slope of the ventilatory response to carbon dioxide was reduced by 22% in the first 2 h after temazepam 40 mg, but this was not statistically significant.

Oral temperature was measured in nine subjects and a significant decrease in temperature was noted 2 h after temazepam 40 mg (fig. 1). The subjects who commented on the cold, seven receiving temazepam 40 mg and five temazepam 20 mg, found this to be the

TABLE III. *Effects of temazepam on the ventilatory response to carbon dioxide. Results are mean values for 12 volunteers*

Treatment	Change in slope (litre kPa^{-1})			Displacement at 30 litre minute volume (kPa)		
	1 h	2 h	3 h	1 h	2 h	3 h
Temazepam 40 mg	−3.92	−3.93	−2.97	+0.65	+0.55	+0.46
Temazepam 20 mg	−1.96	−1.98	−0.14	+0.23	+0.48	+0.28
Placebo	−0.56	−0.50	−0.37	+0.02	+0.16	+0.11
F	1.50	2.95	1.54	3.82	2.80	1.30
Significance	$P < 0.3 > 0.2$	$P < 0.1 > 0.05$	$P < 0.3 > 0.2$	$P < 0.05$	$P < 0.2 > 0.1$	$P < 0.3 > 0.2$

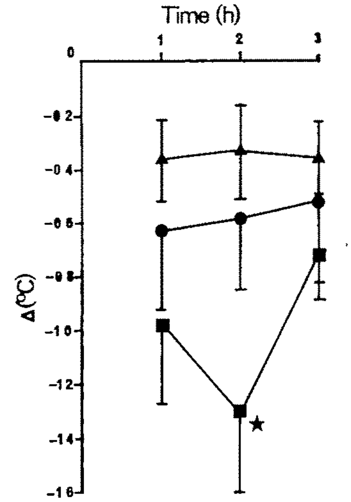

FIG. 1. Effects of temazepam 20 mg (circles), 40 mg (squares) and placebo (triangles) on oral temperature in volunteers. $^{*}P < 0.05$ compared with placebo.

most distressing side-effect. The ambient temperature in the laboratory was 19–21°C throughout the trial.

Both tests of cognitive function, digit symbol substitution and deleting *e* produced strikingly similar results (figs 2A and B). Temazepam 40 mg decreased the number of digits substituted up to and including 2.5 h after administration. Temazepam 20 mg caused a significant decrease in performance only at 0.5 h after administration. Deleting *e* was slightly less sensitive, significant decreases in performance being found 0.5 and 1.5 h after temazepam 40 mg. The number of mistakes made in both of these tests depended more upon the subject than on the drug taken.

More prolonged effects of temazepam were seen in the pursuit rotor test, the deficit in performance being still significant 3.5 h after administration of temazepam 40 mg (fig. 3). Only the results for the 40-rev min^{-1} speed are illustrated. Mean and SEM have been calculated, but preliminary experiments suggested that performance on the pursuit rotor was not normally distributed and thus significance was assessed using the Mann–Whitney *U* test. Qualitatively similar results were obtained at other speeds of the rotor, although the greatest changes were seen at the speed illustrated. At the slowest speed most subjects could maintain contact with the target for a full minute, whilst at the fastest speed contact was often less than 1 s even without the drug. Temazepam 20 mg caused a significant deterioration in pursuit rotor performance 0.5 h after administration.

Two subjects, nos 9 and 12, both small females, exhibited extreme reactions to the drug. Subject no. 9 became extremely excitable and on the evening following temazepam 40 mg exhibited uncharacteristic aggressive behaviour. Subject no. 12 was totally incapable of co-operating in the tests for 1 h following the same dose of temazepam.

Memory deficits were seen only with the large dose of temazepam. This was characterized by almost complete lack of recall of any task undertaken 0.5–2 h after administration of temazepam. Complete recall of the order of drawing symbols was found in subjects given placebo or temazepam 20 mg, but was absent in subjects given temazepam 40 mg.

DISCUSSION

The prompt onset and short duration of the hypnotic actions of temazepam in this study correlate with the pharmacokinetic information on this drug when administered in a soft gelatin capsule (Fuccella et al., 1977; Fuccella, 1979).

Temazepam depressed the ventilatory response to carbon dioxide, an effect which appeared to increase

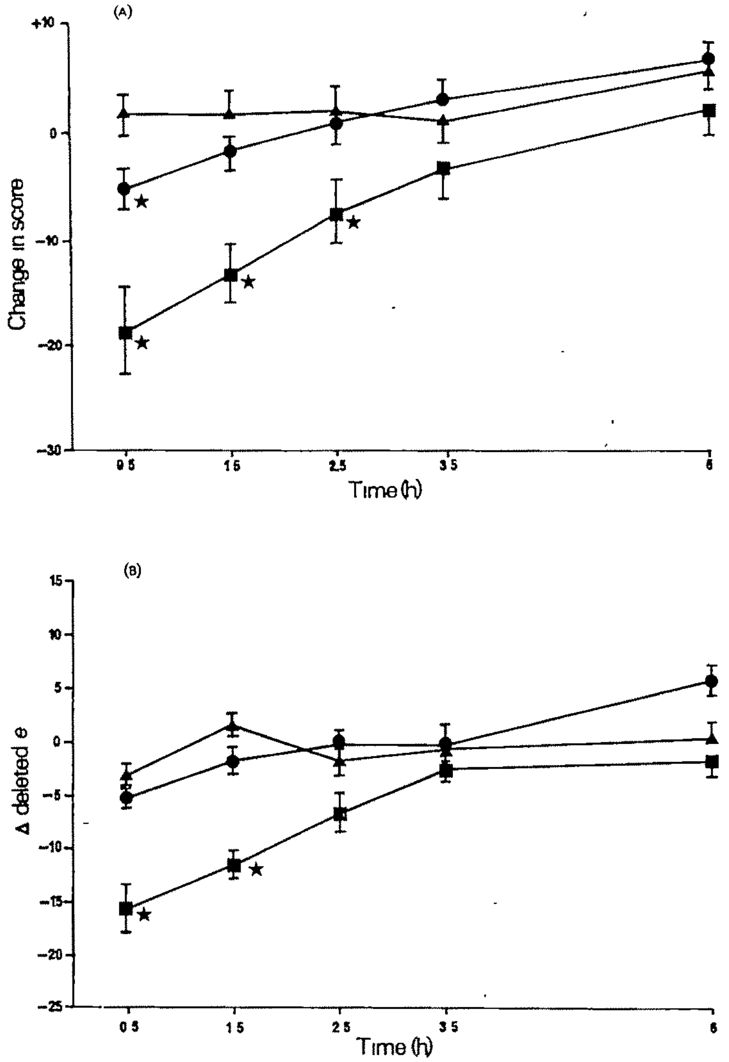

FIG. 2. Effect of temazepam 40 mg (squares), 20 mg (circles) and placebo (triangles) on cognitive function tests. A Digit substitution; B deleting *e*. Values are mean change from pre-drug score (± SEM). *$P < 0.05$ when compared with placebo changes.

with increasing dose. Using a similar experimental design, Utting and Pleuvry (1975) showed that diazepam 5 mg orally caused a displacement of the ventilatory response to carbon dioxide of the same proportions. Thus temazepam, at least in the larger dose, would appear to offer no advantages over diazepam as a hypnotic for patients with obstructive lung disease.

Hypnotic drugs may be associated with the production of hypothermia (Reuler, 1978) and benzodiazepines have been implicated (Irvine, 1966). However, the decrease in body temperature produced by temazepam 40 mg in this study was surprising, as the volunteers were relatively young, actively doing tasks for 10 min in every 30 min and insisted on wearing extra clothing as the trial progressed. This raises the question of the advisability of prescribing temazepam to patients with impaired ability to increase heat production or to prevent heat loss. The subjective feeling of cold which distressed our volunteers after taking temazepam had not been reported in previous trials using diazepam (Utting

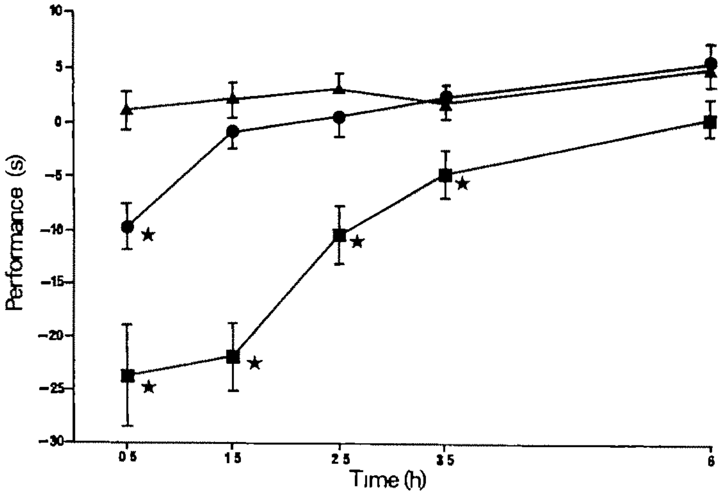

FIG. 3. Effect of temazepam 40 mg (squares), 20 mg (circles) and placebo (triangles) on pursuit rotor performance at 40 rev min^{-1}. Values are expressed as mean change in contact time with target from pre-drug results (±SEM). $^*P < 0.05$ when compared with placebo values.

and Pleuvry, 1975) and lorazepam (Dodson et al., 1976).

Deficits in cognitive function and psychomotor performance have been reported at 3 h after administration of temazepam 30 mg (Roth et al., 1979). These authors found that cognitive function tests were more affected by hypnotic drugs than were psychomotor tests. In the present study we have found that the effects of temazepam lasted longer on the pursuit rotor test (psychomotor) than on the digit substitution test (cognitive function). This may indicate a difference between temazepam and other hypnotic agents or that the pursuit rotor is a more sensitive psychomotor test than those used by Roth and colleagues (1979). In view of the prolongation of psychomotor deficits by temazepam 40 mg beyond 3.5 h it would seem that this dose of temazepam is excessive if an ultra-short-acting hypnotic is required.

ACKNOWLEDGEMENTS

We would like to thank Dr T. V. A. Harry of John Wyeth and Brother Ltd for supplies of temazepam and placebo. We are also indebted to Dr Paul Silverman, now in the Department of Pharmacology, University of Jos, Nigeria, for advice on some of the psychological tests.

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EFFETS RESPIRATOIRES ET PSYCHOLOGIQUES DU TEMAZEPAM ADMINISTRE PAR VOIE BUCCALE A DES VOLONTAIRES

RESUME

On a examiné au cours d'une comparaison à double inconnue effectuée sur 12 volontaires en bonne santé, et à l'aide d'un placebo, les facteurs temps et action des effets du témazépam, administré à raison de 40 mg et de 20 mg,

sur la respiration, la pression artérielle, la température mesurée dans la bouche, la faculté cognitive, les performances psychomotrices et les observations subjectives. Le témazépam administré à raison de 40 mg a provoqué un déplacement significatif de la réaction de la respiration au gaz carbonique 1 h après son administration, de même qu'une diminution de la température prise dans la bouche 2 h après son administration. Des déficiences dans la faculté cognitive étaient toujours apparentes 1,5 h et 2,5 h après l'administration et les performances psychomotrices n'étaient toujours pas équivalentes à celles des témoins 3,5 h plus tard. Cependant, la plupart des sujets se sont sentis normaux au bout de 2,5–3 h. Le témazépam administré à raison de 20 mg a eu des effets significatifs sur la faculté cognitive et sur les performances psychomotrices, mais seulement pendant la première heure qui a suivi l'administration.

RESPIRATORISCHE UND PSYCHOLOGISCHE EFFEKTE VON ORAL VERABREICHTEM TEMAZEPAM BEI FREIWILLIGEN

ZUSAMMENFASSUNG

Bei einem Doppelblindvergleich mit einem Plazebo wurde der zeitliche Wirkungsablauf von Temazepam 40 und 20 mg auf Atmung, arteriellen Druck, Mundtemperatur, Erkennungsfunktion, psychomotorische Leistung, und subjektive Beobachtungen bei 12 gesunden Freiwilligen untersucht. Temazepam 40 mg bewirkten Verdrangung der ventilatorischen Reaktion auf Kohlendioxyd eine Stunde nach der Verabreichung, und ein Absinken der oralen Temperatur 2 Stunden nach Verabreichung. Störungen der Erkennungsfunktion waren 1,5 und 2,5 Stunden nach der Verabreichung erkennbar, und die psychomotorische Leistung hatte 3,5 Stunden nach Verabreichung den Kontrollwert noch nicht erreicht. Doch die meisten Versuchspersonen fuhlten sich 2,5 bis 3 Stunden nach der Verabreichung wieder normal. Temazepam 20 mg hatten signifikante Wirkungen auf Erkennungsfunktion, und auf psychomotorische Leistung nur während der ersten Stunde nach der Verabreichung.

EFECTOS RESPIRATORIOS Y SICOLOGICOS DE LA TEMAZEPAM ORAL EN VOLUNTARIOS

SUMARIO

En una prueba comparativa de doble anonimato con placebos que se efectuó en 12 voluntarios sanos, se examinaron los efectos en el transcurso del tiempo, de temazepam de 40 mg y de 20 mg, al respecto de la respiración, presión arterial, temperatura oral, función cognoscitiva, ejecución sicomotora y observaciones subjetivas. Temazepam de 40 mg causaron un desplazamiento significativo de la respuesta de desplazamiento del dióxido de carbono, 1 h después de su administración y una disminución de la temperatura oral 2 h después de la administración. Entre 1,5 y 2,5 h después de la administración, seguían siendo aparentes las deficiencias de la función cognoscitiva y la ejecución sicomotora no igualó a las de control después de 3,5 h. No obstante, la mayoría de los sujetos se sintieron normales después de 2,5 a 3 h. Temazepam de 20 mg afectaron de forma significativa la función cognoscitiva y la ejecución sicomotora sólo durante la primera hora después de la administración.

Br. J. Anaesth. (1980), **52**, 907

I.V. MIDAZOLAM AS AN INDUCTION AGENT FOR ANAESTHESIA: A STUDY IN VOLUNTEERS

A. FORSTER, J.-P. GARDAZ, P. M. SUTER AND M. GEMPERLE

SUMMARY

The central nervous and cardiovascular effects of midazolam 0.15 mg kg^{-1} were studied in 20 healthy, unpremedicated volunteers (10 male and 10 female). No important side-effects were noted and the venous tolerance to midazolam was excellent. Three minutes after injection mean systolic arterial pressure decreased from $121 \pm$ (SEM) 2 mm Hg to $115 \pm$ (SEM) 2 mm Hg and diastolic pressure from 78 ± 2 to 70 ± 2 mm Hg ($P < 0.05$), and these effects persisted for at least 20 min. Heart rate increased from 77 ± 4 beat min^{-1} to 90 ± 3 and 88 ± 3 beat min^{-1} 1 and 3 min after the injection ($P < 0.05$). Anterograde amnesia (40 ± 3 min duration) and drowsiness (lasting 128 ± 23 min) were observed in all subjects. Loss of the eyelash reflex and apnoea were observed more often in the male group than in the female subjects. Midazolam 0.15 mg kg^{-1} was not sufficient to induce anaesthesia reliably in healthy unpremedicated volunteers.

Midazolam (Ro 21-3981), a new water-soluble benzodiazepine which can be used for the induction of anaesthesia, has two important advantages over diazepam: a short duration of action and absence of vascular irritation when administered i.v. (Conner, Katz and Pagano, 1978; Fragen, Gahl and Caldwell, 1978; Reves et al., 1979). The effects of the administration of midazolam i.v. on the central nervous and cardiovascular systems were determined in healthy volunteers and an assessment of the use of this drug as an induction agent for general anaesthesia was made.

SUBJECTS AND METHODS

Twenty volunteers, 10 female and 10 male (mean age 33 ± 1.5 yr (mean $\pm$ SEM)), weighing 64.2 ± 1.7 kg were studied. Informed consent was obtained and the committee for ethics in human research of our institution approved the programme. The subjects had neither previous medical problem nor took regular medication or alcohol. Each volunteer was fasted for at least 12 h before the beginning of the study which was undertaken before 10 a.m. A Teflon cannula was inserted in a vein on the dorsum of the left hand and a solution of 5% dextrose 100 ml h^{-1} was administered. The e.c.g. and arterial pressure (cuff on right arm) were monitored.

The subjects rested for 30 min in the supine position, and then systolic and diastolic arterial pressures were measured by auscultation (mean arterial pressure was calculated as diastolic pressure + one-third of the pulse pressure). Heart rate and respiratory frequency were determined also. At time zero midazolam maleate 0.15 mg kg^{-1} in a 0.25% solution was injected i.v. over 15 s and the cannula was flushed using the i.v. infusion while the subject was asked to count aloud. Arterial pressure, heart rate and respiratory frequency were measured again at 1, 3, 5 and 20 min after injection of the drug.

The following observations were noted: time to the onset of dysarthria; time to cessation of counting; time and duration of disappearance of the eyelash reflex; onset and duration of apnoea; time of opening the eyes spontaneously; duration of sleep (time between injection of the drug and the moment at which the subjects remained awake and kept the eyes open without stimulation); duration of subjective drug effect.

Retrograde amnesia, defined as a lack of recall before injection, was tested by showing the volunteer a playing card and a written number 30 s before the administration of the drug. As soon as the subject became rousable, he was asked to state the card and number shown to him before injection.

Anterograde amnesia, defined as a lack of recall after the administration of the drug, was tested by showing a card and a number to the volunteer. As soon as his eyelash reflex had returned he had to identify them aloud. The recall was tested 1 min

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0007-0912/80/090907-05 $01.00

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after the initial presentation. This procedure was repeated every 5 min, each time with a different number and card. The time at which the volunteer started to recall was accepted as being the end of anterograde amnesia.

A neurological scoring system (table I) was established to compare the overall effects of midazolam on the central nervous system and the differences between males and females.

TABLE I. *Neurological scoring system. Maximum possible score = 22; minimum possible score = 4*

		Score
(1) Duration of dysarthria	<30 s	1
	30–60 s	2
	>60 s	3
(2) Time of cessation of counting	<100 s	2
	100–300 s	1
	>300 s	0
(3) Loss of eyelash reflex	yes	2
	no	0
(4) Apnoea	yes	2
	no	0
(5) Duration of closure of eyes	>10 min	2
	<10 min	1
	never closed	0
(6) Opening of eyes on command	yes	0
	no	2
(7) Duration of sedation	<30 min	1
	30–60 min	2
	>60 min	3
(8) Duration of subjective effect	<4 h	1
	4–8 h	2
	>8 h	3
(9) Duration of amnesia	<30 min	1
	30–45 min	2
	>45 min	3

Twenty-two minutes after injection of the drug, the volunteer was asked to stand up and walk and his ability was assessed as good, fair or bad. After 60 min, in order to test the subject's concentration, he was asked to read a written text aloud. The reading was assessed good, fair or bad. Twenty-four hours after the experiment, each volunteer had to signify whether the experience had been acceptable, fair or unacceptable. Signs and symptoms of venous irritation were sought at 48 h. Statistical analysis was carried out using the Student's *t* test and the Chi-square test. All data are expressed as mean ± SEM.

RESULTS

The cardiovascular effects of midazolam 0.15 mg kg^{-1} i.v. over 15 s are summarized in figure 1. The systolic and diastolic arterial pressures decreased 3 min after the injection from 121 ± 2 to 115 ± 2 mm Hg and 78 ± 2 to 70 ± 2 mm Hg respectively ($P < 0.05$). These decreases in arterial pressure remained constant for at least 20 min. The heart rate increased 1 min after the administration of the drug, from 77 ± 4 to 90 ± 3 beat min^{-1} ($P < 0.05$) and lasted for 5 min. When the subjects were asked to stand up 22 min after the injection, the mean arterial pressure did not change significantly (86 ± 2 to 82 ± 2 mm Hg), whereas the heart rate increased from 78 ± 3 to 89 ± 3 beat min^{-1} ($P < 0.05$).

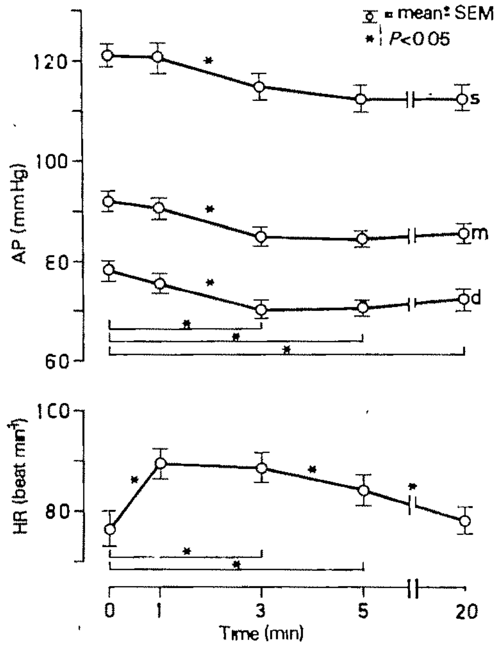

FIG. 1. Variations of systolic (s), mean (m), diastolic (d), arterial pressures (AP) and heart rate (HR) after i.v. injection of midazolam maleate 0.15 mg kg^{-1} in 20 healthy volunteers.

The effects of midazolam on the central nervous system are summarized in figure 2. All time data are related to the time of beginning the injection. Dysarthria occurred in all volunteers, at a mean time of 49 ± 4 s after injection. Seventeen of the 20 subjects stopped counting at 120 ± 22 s; the remaining three continued counting for more than 5 min. Ten of the 20 subjects (seven male and three female) lost the eyelash reflex at 164 ± 42 s, for a duration of 304 ± 104 s. We observed no retrograde amnesia; every volunteer remembered the card and number shown to him before the injection. However, anterograde amnesia of 40 ± 3 min duration occurred in all

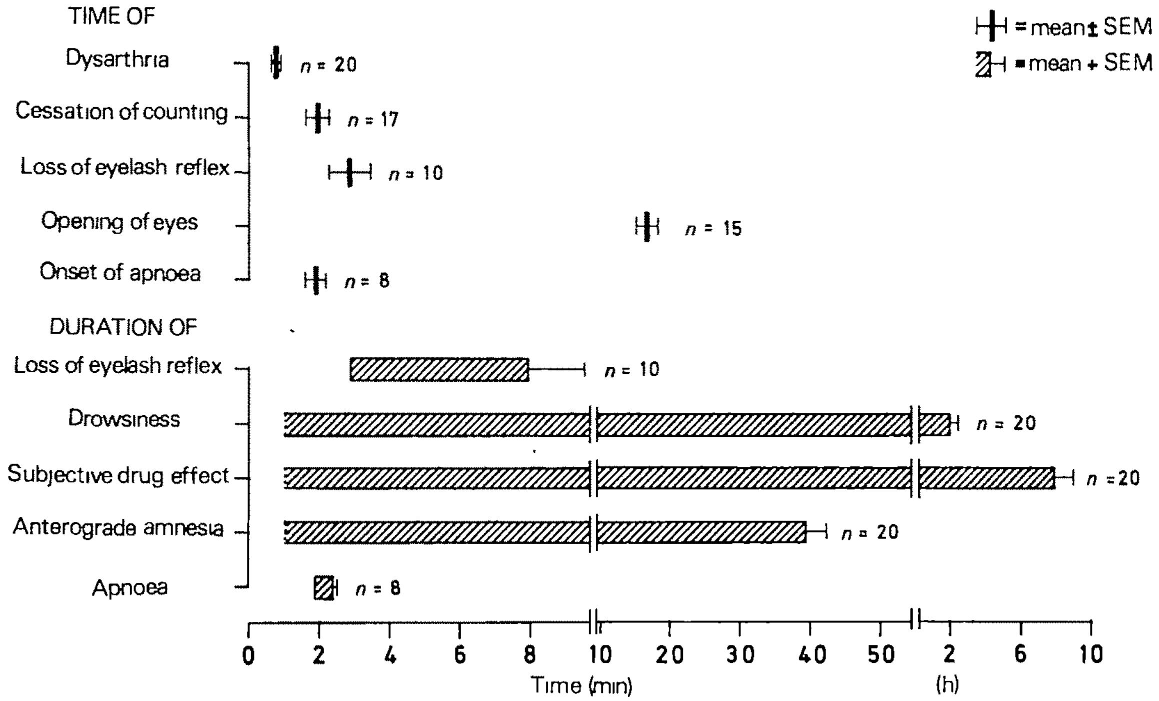

FIG. 2. Onset and duration of central nervous effects after i.v. injection of midazolam 0.15 mg kg^{-1} i.v. in 20 healthy subjects.

subjects. Drowsiness lasted for 128 ± 23 min and the sensation of being under the influence of the drug for 6.7 ± 0.8 h. These symptoms were experienced by every subject. Apnoea occurred in seven of the 10 males and only in one female at 114 ± 19 s and lasted for 30 ± 4 s. Fifteen of the 20 volunteers opened the eyes spontaneously 17 ± 2 min after the administration of the drug.

The effects of the drug were said to be acceptable by 12 of the 20 volunteers and fair by eight others. Twenty-two minutes after the injection, steadiness (walking test) was fair in 12 volunteers and good in eight others. Diplopia occurred in half of the subjects and lasted for about 20 min. After 1 h concentration (reading test) was bad in four subjects, fair in four and good in the other 12. A mild burning at the injection site was noted on three occasions, but no signs or symptoms of venous irritation could be found at 48 h.

Males and females responded differently to the administration of midazolam (fig. 3). The duration of anterograde amnesia was 46 ± 5 min in males and 33 ± 3 min in females. The sensation of being under the influence of the drug lasted for 8 ± 1 h in males and 5.3 ± 1 h in females; apnoea occurred in 70% of the male and in only 10% of the female subjects. The eyelash reflex disappeared in seven of 10 males and three of 10 females. Nine of 10 males closed the eyes after the administration of the drug and reopened them spontaneously after 20 ± 3 min, whereas six of 10 females closed them and reopened them after 12 ± 3 min. The differences in these data between male and female subjects are statistically and clinically significant. If the overall effects on the central nervous system are compared between males and females using the neurological score (table I), the male group had a significantly greater score (16.6 ± 1.1) than the female group (11.0 ± 1.0).

DISCUSSION

The present study shows that midazolam 0.15 mg kg^{-1} produced drowsiness and amnesia in all healthy young volunteers examined. Other effects on the central nervous system were not observed repeatedly (fig. 2). There was no retrograde amnesia, but anterograde amnesia similar to that produced by diazepam (Dundee and Haslett, 1970) was impressive since none of the subjects remembered standing up and walking 22 min after the injection. The loss of the

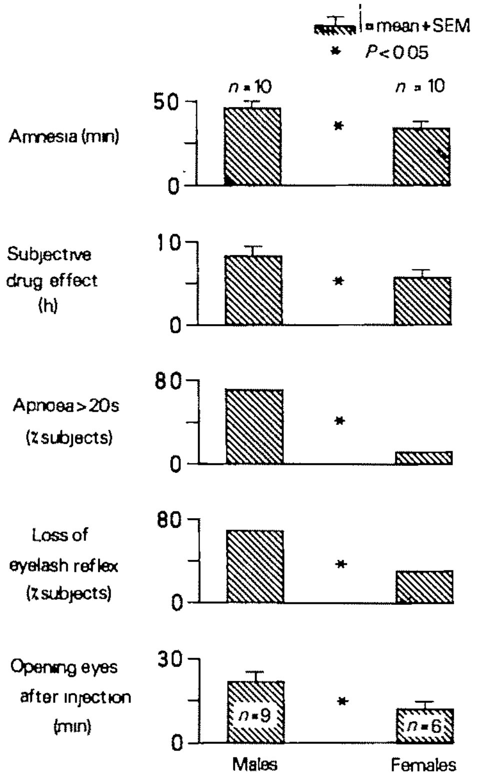

FIG. 3. Difference of central nervous system effects between males and females after i.v. injection of midazolam 0.15 mg kg^{-1} i.v.

eyelash reflex, a useful sign during the induction of anaesthesia, was observed in only 50% of the subjects. These data confirm those of Reves, Corssen and Holcomb (1978) and suggest that midazolam 0.15 mg kg^{-1} is inadequate to induce anaesthesia reliably in unpremedicated young subjects. It has been shown that a larger dose (0.2 mg kg^{-1}) provides a satisfactory induction of anaesthesia in 100% of unpremedicated patients (Reves, Corssen and Holcomb, 1978).

Our study shows that the i.v. administration of midazolam 0.15 mg kg^{-1} produces a statistically significant but clinically unimportant decrease in arterial pressure and an increase in heart rate in healthy volunteers. Other investigations in older but healthy patients confirm our findings (Conner, Katz and Pagano, 1978; Fragen, Gahl and Caldwell, 1978). At larger doses or in patients specially at risk midazolam could possibly cause a greater cardiovascular disturbance.

The difference in the sensitivity to midazolam between males and females was significant for five important neurological indices (fig. 3) and it was confirmed by the neurological scoring system applied. Our study does not provide data to explain this difference. It could be the result of a true decreased sensitivity to midazolam or of an increased volume of distribution in female subjects. This difference requires investigation and confirmation by further studies.

ACKNOWLEDGEMENTS

We would like to thank the residents and nurses of the Department of Anesthesiology for volunteering in this study. Midazolam maleate was kindly supplied by Hoffman-La Roche Inc., Basle, Switzerland. The secretarial assistance of Mrs M. C. Froment and R. Schiavi is gratefully acknowledged.

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ADMINISTRATION DE MIDAZOLAM PAR VOIE INTRAVEINEUSE EN TANT QU'AGENT D'INDUCTION DE L'ANESTHESIE: ETUDE EFFECTUEE SUR DES VOLONTAIRES

RESUME

On a étudié sur 20 volontaires (10 hommes et 10 femmes) en bonne santé, n'ayant reçu aucune prémédication, les effets de 0,15 mg kg^{-1} de midazolam sur le système nerveux central et sur le système cardiovasculaire. On n'a remarqué aucun effet secondaire important et la tolérance veineuse au midazolam a été excellente. Trois minutes après l'injection, la pression systolique artérielle moyenne a baissé de 121 mm Hg±2 (écart type des moyennes) à 115 mm Hg±2 (écart type des moyennes) et la pression diastolique a diminué de 78 mm Hg±2 à 70 mm Hg±2 ($P<0,05$) et ces effets se sont maintenus pendant au moins 20 min. La fréquence cardiaque a augmenté de 77 battements min^{-1}±4 à 90±3 et 88±3 battements min^{-1}; 1 et 3 min après l'injection ($P<0,05$). On a constaté sur tous les sujets une amnésie antérograde (d'une durée de 40 min±3 min) et une somnolence diurne (durant 128 min±23 min). On a observé plus souvent sur le groupe d'hommes que sur le groupe de femmes la perte du réflexe de cillement et de

l'apnée. Le midazolam administré à raison de 0,15 mg kg^{-1} n'a pas été suffisant pour induire l'anesthésie d'une manière fiable à des volontaires en bonne santé n'ayant reçu aucune prémédication.

INTRAVENÖSES MIDAZOLAM ZUR NARKOSEEINLEITUNG: EINE STUDIE AN FREIWILLIGEN

ZUSAMMENFASSUNG

Die Zentralnerven- und Kardiovaskuläreffekte von 0,15 mg kg^{-1} Midazolam wurden an 20 gesunden, nicht vorbehandelten Friewilligen (10 männlich, 10 weiblich) studiert. Keine wichtigen Nebenerscheinungen wurden bemerkt, und die venöse Toleranz auf die Droge war ausgezeichnet. Drei Minuten nach der Injektion sank der systolische Arteriendruck von 121± (SEM) 2 mm Hg auf 115± (SEM) 2 mm Hg, und der diastolische Druck von 78±2 auf 70±2 auf 70±2 mm Hg ($P<0,05$), und diese Effekte dauerten wenigstens 20 min an. Pulszahl stieg von 77±4 auf 90±3 und auf 88±3 Schläge min^{-1} 1 und 3 Minuten nach der Injektion ($P<0,05$). Anterograde Amnesie (40±3 min Dauer) und Schläfrigkeit (Dauer 128±23 min) wurden bei allen Personen beobachtet. Verlust des Lidreflexes und Apnoe wurden bei den Männern häufiger als bei den Frauen beobachtet. Midazolam in Höhe von 0,15 mg kg^{-1} war nicht ausreichend, um bei gesunden, nicht vorbehandelten Freiwilligen Narkose einzuleiten.

MIDAZOLAM INTRAVENOSA CUAL UN AGENTE DE INDUCCION DE ANESTESIA: UN ESTUDIO EFECTUADO CON VOLUNTARIOS

SUMARIO

Se estudiaron los efectos cardiovasculares y sobre el sistema nervioso central, de 0,15 mg kg^{-1} de midazolam en 20 voluntarios sanos y sin previa medicación (10 hombres y 10 mujeres). No se apreciaron efectos secundarios importantes y la tolerancia venosa al midazolam fue excelente. Tres minutos después de la inyección la presión sistólica arterial disminuyó desde 121±2 mm Hg hasta 115±2 mm Hg y la presión diastólica disminuyó desde 78±2 mm Hg hasta 70±2 mm Hg ($P<0,05$) y estos efectos perduraron durante, por lo menos, 20 minutos. El ritmo cardiaco aumentó desde 77±4 latidos min^{-1} hasta 90±3 y 88±3 latidos min^{-1}, 1 y 3 min después de la inyección ($P<0,05$). En todos los sujetos se observó amnesia de anterogrado (40±3 min de duración) y adormecimiento (durante 128±23 min). En el grupo de hombres se observó apnea y pérdida de reflejo en el párpado con más frecuencia que en las mujeres. No fueron suficientes 0,15 mg kg^{-1} de midazolam para inducir una anestesia fiable en voluntarios sanos y sin previa medicación.

Br. J. Anaesth. (1980), **52**, 913

PHARMACOKINETICS OF THIOPENTONE IN A GROUP OF YOUNG WOMEN AND A GROUP OF YOUNG MEN

J. H. CHRISTENSEN, F. ANDREASEN AND J. A. JANSEN

SUMMARY

The average induction dose of thiopentone did not differ significantly when eight young women were compared with eight young men. In neither group did the dose increase with increased body weight. Clearance of thiopentone from venous blood was described by a three-compartment open model. The average volumes of V_1 and V_3 were greater in the females, but only the difference between the V_3 values was significant ($P < 0.05$). Significant correlations ($P < 0.01$) were found between the initial drug concentrations and the k_{12} values. The slopes of the regression lines were 0.0029 for the women and 0.0038 for the men ($0.1 < P < 0.2$). It is suggested that the redistribution rate constant k_{12} is predominant in determining the sleep dose rather than the initial distribution volume V_1.

It is accepted that the age, sex and body weight of a patient influence the dose of thiopentone required to maintain anaesthesia (Dundee, 1954). When investigating the dose of thiopentone necessary for the induction of anaesthesia, Christensen and Andreasen (1978) found that, although the apparent difference between men and women was not significant when individual age groups were compared, the average dose for all the men was significantly greater than that for the women. Moreover, there was a considerable individual variation in groups of patients comparable with respect to age, sex, body weight and surgical disease.

In the only complete pharmacokinetic study of thiopentone in patients Ghoneim and Van Hamme (1978) studied the effect of enflurane, nitrous oxide and surgery on the pharmacokinetics of the drug.

The present investigation compared a group of young women with a group of young men with respect to dose and to pharmacokinetic data obtained by conventional compartmental analysis based on concentrations of thiopentone in peripheral venous blood.

Since the individual variation may be related to the method of drug administration, the drug was administered exactly as in our previous study of 1978.

PATIENTS AND METHODS

Eight male and eight female patients gave informed consent to the study. The age range was 20–40 yr. The women underwent minor gynaecological operations, the men orthopaedic procedures. The diseases were not of an acute nature. No patient showed evidence of a disease other than the surgical disease condition.

Pethidine 1 mg plus diazepam 0.1 mg per kg body weight and atropine 0.5 mg were given i.m. 0.5–1 h before the induction of the anaesthesia. Anaesthesia was induced with thiopentone as described in detail below. Suxamethonium 100 mg was given to facilitate tracheal intubation and anaesthesia was maintained with nitrous oxide in oxygen and halothane. The lungs were ventilated artificially and every anaesthetic was administered by the same anaesthetist (J.H.C.). The duration of anaesthesia was 55–220 min for the men and 50–120 min for the women.

The thiopentone solution was injected to a vein on the back of the hand until the eyelash reflex was obtunded. The first 250 mg was given over 25 s. After that repeated doses of 50 mg were injected over 2 s every 20 s. Before each injection the patient was examined to determine the presence or absence of the eyelash reflex. The total dose administered (induction dose) was injected over 85–145 s.

Blood samples for the determination of thiopentone were withdrawn from an indwelling catheter placed in a large cubital vein in the arm opposite to the

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injection. A control sample was taken before induction. The first sample was drawn 40 s after the last injection of thiopentone (20 s after the observation of an absent eyelash reflex). Further samples were taken at 5, 10, 20, 30, 45, 60 and 90 min and 2, 3, 4, 6, 8, 12–14 and 18–20 h. The blood was allowed to coagulate; serum was obtained by centrifugation and kept refrigerated for 1–2 days before analysis.

Thiopentone was analysed by high performance liquid chromatography (Christensen and Andreasen, 1979). The sensitivity of the method was 0.1 $\mu g\ ml^{-1}$. None of the drugs given to the patients interferes with the assay.

Calculations of pharmacokinetic data

A three-compartment open model with elimination from the central compartment only was used to describe the disappearance of thiopentone from the serum. The model was fitted to the time (t)–serum concentration (C_S) data by numerical solution of coupled differential equations describing the concentration changes in the central compartment (equation (1)), in the "shallow" peripheral compartment (equation (2)) and in the "deep" peripheral compartment (equation (3)):

$$\frac{dC_1}{dt}=\frac{k'_{01}}{V_1}-(k_{10}+k_{12}+k_{13})C_1+k_{21}C_2+k_{31}C_3 \qquad (1)$$

$$\frac{dC_2}{dt}=k_{12}C_1-k_{21}C_2 \qquad (2)$$

$$\frac{dC_3}{dt}=k_{13}C_1-k_{31}C_3 \qquad (3)$$

The meanings of V_1, k_{10}, k_{12}, k_{21}, k_{13} and k_{31} are as accepted normally and k'_{01} is the infusion rate. The value of k'_{01} was changed with time during the numerical solution according to the administration schedule. The hybrid rate constants π, α and β were calculated as the roots of equation (4):

$$x^3-ax^2+bx-c=0 \qquad (4)$$

where the values of a, b and c appear from equations (5), (6) and (7) (Gibaldi and Perrier, 1975):

$$a=k_{10}+k_{12}+k_{21}+k_{13}+k_{31} \quad (=\pi+\alpha+\beta) \qquad (5)$$

$$b=k_{10}k_{21}+k_{13}k_{21}+k_{10}k_{31}+k_{21}k_{31}+k_{31}k_{12} \quad (=\pi\alpha+\pi\beta+\alpha\beta) \qquad (6)$$

$$c=k_{10}k_{21}k_{31} \quad (=\pi\alpha\beta) \qquad (7)$$

The main differences between the serum concentration–time curve obtained in the present study and the serum concentration–time curves utilized in the majority of other studies is that we have given repeated bolus injections of the drug with short intervals initially and took the first sample of blood from an arm vein 40 s after the last injection. A possible influence, on the initial distribution of the drug, of individual differences in haemodynamics would not be reflected in the calculated parameters if no blood concentrations were measured during the first few minutes. Therefore, we performed the calculations with inclusion of the first (40-s) blood sample as well as with its exclusion (beginning with the 5-min value).

RESULTS

The dose of thiopentone required to induce anaesthesia did not increase significantly with the body weight of the patients (fig. 1). For neither men nor women is the slope of the regression line different from 0. As is shown in figure 1 and table I, the average dose was greater in men. However, if the dose is adjusted for the differences in body weight, this apparent difference disappears.

TABLE I. *Average i.v. doses of thiopentone ($\pm$ SD) necessary for induction of anaesthesia in eight young women and in eight young men*

	Women	Men
Dose injected (mg)	319 ± 37	388 ± 52
Dose injected (mg per kg body weight)	5.43 ± 0.64	5.25 ± 1.05

The concentration of thiopentone in serum in one of the patients (▼ table III) is shown as a function of time in the semilogarithmic plot in figure 2. Similar relationships between the serum concentrations and time were found for all 16 patients and in all patients the decline of the serum concentration could be described by a three-compartment open model—and not by a one- or a two-compartment model.

The pharmacokinetic data obtained by analysis of the serum concentration curves are listed in tables II and III. The average values for V_1 and V_3 were greater in the female group, but only the difference between the V_3 values was significant ($P<0.05$). The average values of the serum half-lives were greater in the women than in the men, but only the difference

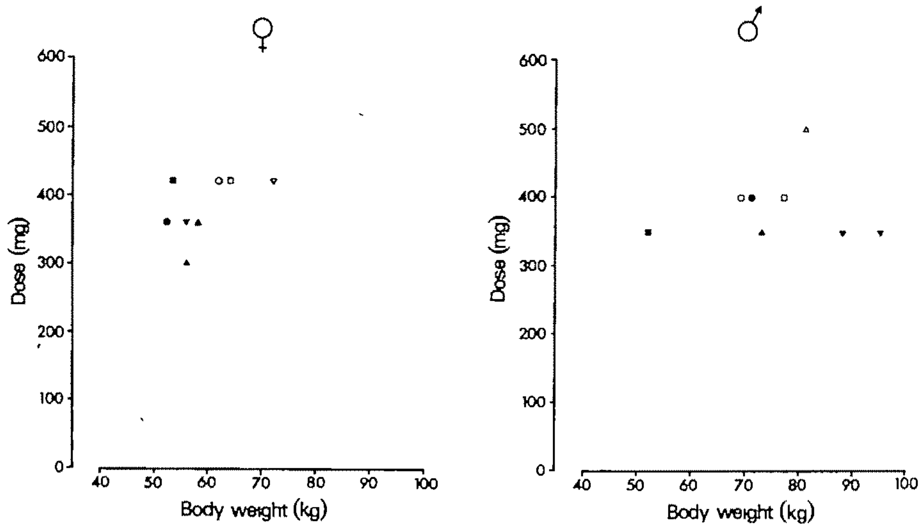

FIG. 1. Relationship between body weight and the induction dose of thiopentone in eight male and eight female patients.

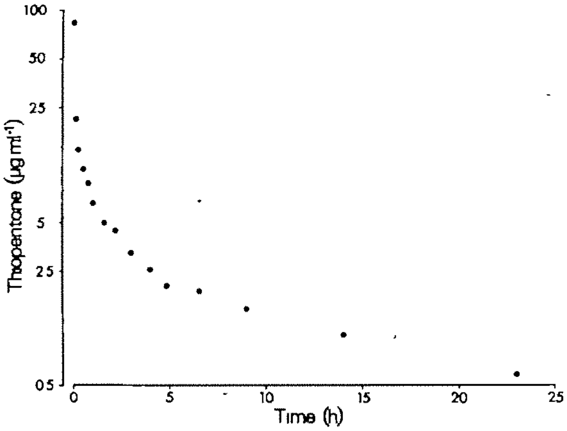

FIG. 2. The serum concentration of thiopentone as a function of time for patient ▼ in table III.

between the $T_{\frac{1}{2}}{}^{\beta}$ values was statistically significant ($P < 0.05$, Mann–Whitney). Significant correlations ($P < 0.01$) were found between the initial values of the serum concentration and the k_{12} values for both women and men (fig. 3). The apparent difference in slope (slope 0.0029 for women and 0.0038 for men) was not statistically significant ($0.1 < P < 0.2$). The averages of the k_{12} values were not significantly different either. It was tested whether a three-compartment model could be used if the initial serum concentration value was disregarded. For both groups of patients, a three-compartment model could still be used to describe the serum concentration curves, but significant correlations between the initial serum concentration (5 min) and k_{12} were no longer present.

TABLE II. *Pharmacokinetic parameters for thiopentone in eight male patients*

Patient	Age (yr)	Body weight (kg)	V_1 (litre)	V_2 (litre)	V_3 (litre)	k_{12} (min^{-1})	k_{13} (min^{-1})	k_{10} (min^{-1})	$T_{\frac{1}{2}}{}^{\pi}$ (min)	$T_{\frac{1}{2}}{}^{\alpha}$ (min)	$T_{\frac{1}{2}}{}^{\beta}$ (min)	*Cl* (litre min^{-1})
□	36	77	3.88	10.59	30.57	0.237	0.060	0.035	1.7	28	296	0.136
■	21	52	4.58	5.97	19.38	0.169	0.042	0.018	2.1	23	305	0.082
○	26	69	3.41	10.45	21.78	0.311	0.066	0.034	1.4	25	262	0.116
●	20	71	14.46	10.16	32.31	0.048	0.008	0.011	5.5	57	388	0.159
△	39	81	6.61	22.93	44.32	0.128	0.021	0.025	3.4	71	473	0.165
▲	23	73	3.04	10.68	39.79	0.257	0.073	0.057	1.6	28	313	0.173
▽	29	88	5.97	12.09	22.35	0.198	0.031	0.032	2.0	31	206	0.191
▼	40	95	16.97	18.11	42.58	0.081	0.021	0.017	4.1	53	373	0.288

TABLE III. *Pharmacokinetic parameters for thiopentone in eight women*

Patient	Age (yr)	Body weight (kg)	V_1 (litre)	V_2 (litre)	V_3 (litre)	k_{12} (min^{-1})	k_{13} (min^{-1})	k_{10} (min^{-1})	$T_{\frac{1}{2}}^{\pi}$ (min)	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	*Cl* (litre min^{-1})
□	36	64	4.25	9.00	135.49	0.148	0.046	0.011	2.7	43	273	0.047
■	25	53	5.48	6.17	36.07	0.163	0.041	0.022	2.0	23	368	0.121
○	25	62	11.00	14.24	53.54	0.088	0.016	0.011	4.0	56	626	0.121
●	25	52	10.44	17.90	53.47	0.101	0.020	0.020	3.7	49	417	0.209
△	23	57	11.12	10.55	43.61	0.058	0.026	0.012	4.9	33	407	0.133
▲	31	56	12.82	23.35	165.20	0.063	0.019	0.012	5.8	71	1312	0.154
▽	22	72	15.55	9.07	38.30	0.036	0.010	0.011	6.5	49	379	0.171
▼	25	56	2.37	9.02	36.79	0.264	0.067	0.038	1.6	35	501	0.090

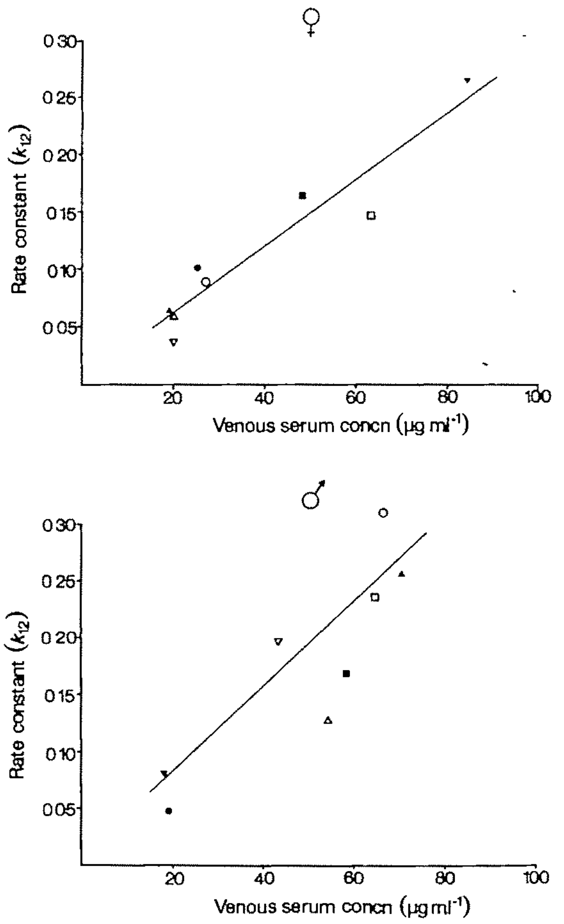

FIG. 3. The initial value of the venous serum concentration of thiopentone as a function of the rate constant k_{12}. The apparent difference in slope between the regression lines for men and women is not statistically significant.

DISCUSSION

Dose–effect relationship

Our comparison of a group of young women with a group of young men showed a greater but not statistically significant sensitivity to thiopentone in women; this apparent difference disappeared when the dose was corrected for differences in body weight. A large individual variation in sensitivity in the groups did not disappear by correction of the dose for differences in body weight (range for the women 4.5–6.6 and for the men 3.6–7.0 mg/kg body weight). Edwards and Ellis (1973) found even larger variation (range 1–4.5 mg kg^{-1}) in induction doses between male Ghanaian patients with a larger age range (mean 34.2 yr ± 11.9 SD) and with different chronic diseases. Becker (1978) gave thiopentone as an infusion to 36 comparable individuals. He found that 26 patients required 10.1 ± 0.5 mg kg^{-1} for induction while in 10 5.8 ± 0.5 mg kg^{-1} was adequate.

The finding in the groups that additional weight does not necessarily mean decreased sensitivity to a given dose may be in good agreement with Wulfsohn and Joshi (1969) who found that the induction dose correlated better with the lean body mass than with the body weight.

Kinetic considerations

Valuable information about the distribution and elimination patterns in the *average* patient have been obtained by measuring thiopentone concentrations in different anatomically or physiologically defined regions. By doing this Price and colleagues (1960) and Bischoff and Dedrick (1968) found excellent agreement between the concentrations actually measured and concentrations predicted—by assuming certain values for flow and volume from data available in the literature. One of our objects was to elucidate and explain the reasons for the large individual variation in response to a given dose of thiopentone. In the present study we found it crucial to utilize fully the interpretation of the curves illustrating the decline in the venous serum concentrations of thiopentone; this method of obtaining information was the only one possible.

For none of our patients could the serum concentration curves be adequately described by a one- or a two-compartment model. However, they could all be described by a three-compartment model. After thiopentone 3.5 mg/kg body weight injected over 30 s, Ghoneim and Van Hamme (1978) found that the kinetics of the venous concentration curve could be described by a three-compartment open model in nine subjects and by a two-compartment model in three subjects. We found that the V_3 values were significantly greater in the women than in the men ($P < 0.05$). Also the terminal serum half-lives were significantly longer in the women (range 4.5–22 h in women and 4–8 h in men). Ghoneim and Van Hamme (1978) found an average elimination half-life of 5.14 h in three young women and three young men.

The individual variation in serum concentration found by us 20 s after the disappearance of the eyelash reflex was as large as the individual variation in dose per kg body weight. Becker (1978) gave thiopentone by i.v. infusion and found that the arterial concentration needed to abolish the eyelash reflex was small and rather constant (22.7 ± 1.7 μg ml^{-1}). We found a considerably greater and not very constant venous concentration 20 s after the disappearance of the eyelash reflex (average 49.8 ± 19.7 μg ml^{-1} in men and 38.6 ± 24.1 μg ml^{-1} in women). The average value found by Becker (1978) was close to our value 5 min after the last injection of thiopentone (4 min and 40 s after the disappearance of the eyelash reflex (21.0 ± 5.7 μg ml^{-1}). Becker (1978) found also that the dose was high and rather variable (see above); he gave 150 mg initially followed by infusion of 90 mg min^{-1} whereas we gave 250 mg initially followed by 150 mg min^{-1} in repeated, rapidly injected doses of 50 mg every 20 s. It seems likely that the slow administration caused a general increase in the dose necessary for induction and nullified the importance of individual variations in the initial distribution phase. This point of view is supported by the significant correlations we found for men and for women between the k_{12} and the venous serum concentrations 20 s after the disappearance of the eyelash reflex. There was no correlation between the k_{12} values, calculated without the initial serum concentration value, and either the initial or the 5-min values. Thus, the omission of the initial value loses valuable information. We suggest that patients with small values of k_{12} will reach the necessary serum concentration sooner than patients with large k_{12} values, who possess the ability to distribute the drug more effectively to organs unimportant for the observed effect.

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PHARMACOCINETIQUE DU THIOPENTONE ETUDIEE SUR UN GROUPE DE JEUNES FEMMES ET DE JEUNES HOMMES

RESUME

La dose moyenne d'induction du thiopentone n'a pas différé de façon significative lorsqu'on a fait une comparaison entre huit jeunes femmes et huit jeunes hommes. La dose n'a été augmentée ni dans un groupe ni dans l'autre en fonction du poids du corps. L'élimination du thiopentone du sang veineux a été décrite par un modèle ouvert à trois compartiments. Les volumes moyens de V_1 et de V_3 ont été plus élevés chez les femmes, mais seul l'écart entre les valeurs de V_3 a été significatif ($P < 0,05$). On a trouvé des corrélations significatives ($P < 0,01$) entre les concentrations initiales du médicament et les valeurs de k_{12}. Les pentes des lignes de régression ont été de 0,0029 pour les femmes et de 0,0038 pour les hommes ($0,1 < P < 0,2$). On laisse entendre que la constante k_{12} du taux de redistribution prédomine dans la détermination de la dose pour le sommeil, plutôt que le volume V_1 de répartition initiale.

DIE PHARMAKOKINETISCHEN AKTIVITÄTEN VON THIOPENTON IN EINER GRUPPE JUNGER FRAUEN UND EINER GRUPPE JUNGER MÄNNER

ZUSAMMENFASSUNG

Die durchschnittliche Narkoseeinleitungsdosis von Thiopenton unterschied sich nicht wesentlich bei einer Gruppe junger Frauen und einer Gruppe junger Männer (jeweils 8). Bei keiner der Gruppen stieg die Dosis bei erhöhtem Körpergewicht. Die Ausscheidung der Droge aus dem venösen Blut wurde mittels eines offenen Modells mit drei Kammern beschrieben. Die Durchschnittsvolumen von V_1 und V_3 waren bei den Frauen grosser, doch war nur der Unterscheid zwischen den V_3 Werten signifikant ($P<0,05$). Signifikante Korrelationen ($P<0,01$) bestanden zwischen den anfänglichen Drogenkonzentrationen und den k_{12} Werten Das Gefälle der Abstiegslinien war 0,0029 bei den Frauen und 0,0038 bei den Mannern ($0,1<P<0,2$). Es wird gefolgert, dass die Wiederverteilungskonstante k_{12} bestimmend bei Feststellung der Schlafdosis ist, eher als das anfängliche Verteilungsvolumen V_1.

FARMACOCINETICAS DE LA TIOPENTONA EN UN GROUP DE MUJERES JOVENES Y EN UN GROUP DE HOMBRES JOVENES

SUMARIO

La dosis media de inducción de tiopentona no fue significativamente diferente cuando se compararon 8 mujeres jovenes con 8 hombres jovenes. En ninguno de los grupos aumentó la dosis en proporción al incremento del peso del cuerpo. La separación de la tiopentona en relación a la sangre venosa se describió mediante un modelo abierto de tres compartimientos. Los volumenes medios de V_1 y V_3 fueron superiores para las mujeres, pero sólo la diferencia entre los valores V_3 fue significativa ($P<0,05$). Se encontraron correlaciones significativas ($P<0,01$) entre las concentradiones iniciales de la droga y los valores de k_{12}. Las pendientes de las líneas de regresión fueron de 0,0029 para las mujeres y de 0,0038 para los hombres ($0,1<P<0,2$). Se sugiere que la constante del ritmo de redistribución, k_{12}, es predominate en lo que se refiere a determinar la dosis correspondiente al sueno en vez del volumen inicial de distribución V_1.

Br. J. Anaesth. (1980), **52**, 919

CAESAREAN SECTION ASSOCIATED WITH GROSS OBESITY

R. HODGKINSON AND F. J. HUSAIN

SUMMARY

The anaesthetic and surgical problems associated with Caesarean section in eight grossly obese patients (weight 150–204 kg) are described. In addition to an increase in the frequency and severity of the complications of obesity, those weighing more than 150 kg present a panniculus which may weigh 70 kg. Extradural analgesia was used for three patients and general anaesthesia for five (two because of fetal distress). One fetus died *in utero* after serious and prolonged arterial hypotension in the mother caused by powerful cephalad retraction of the panniculus (extradural analgesia). General anaesthesia was associated with severe episodes of hypertension in two patients.

Caesarean section in the grossly obese has been reviewed by Sicuranza and Tisdall (1975). Of their 24 patients weighing more than 114 kg, nine (40%) had diabetes mellitus and 12 (50%) had toxaemia and hypertension; twin pregnancy had been diagnosed in two patients and fetal transverse lie in three. The average fetal weight was 4026 g. There was one stillbirth "which possibly could have been avoided if the reluctance to resort to section had not been present".

A weight of approximately three times normal is not only associated with an increased frequency and severity of obstetric complications, but also with special problems created by the massive panniculus, which in one of our patients (no. 7) covered the knees and was estimated to weigh 70 kg. The maternal and perinatal mortality associated with such obesity is high. Of eight parturients weighing 148–203 kg described by Freedman, Wilds and George (1972) each of the two patients delivered by Caesarean section died, one from sepsis and one from pulmonary embolus. A third patient suffered profound shock after vaginal delivery followed by pan-hysterectomy. Two of the babies were stillborn.

Until recently the retraction of the panniculus has been caudad to permit a midline or paramedian incision (Morrow et al., 1977). However, Ahern and Goodlin (1978) reported successful results in four parturients weighing more than 181 kg, by retracting the panniculus cephalad and performing a Pfannenstiel incision. Since the addition of 50–70 kg to the upper abdomen can reduce venous return to the heart and embarrass ventilation, we reviewed eight cases of Caesarean section in patients weighing more than 150 kg at The University of Texas Health Science Center at San Antonio during a period of 30 months. A paramedian or a midline incision was used for seven patients and a Pfannenstiel incision for one patient.

CASE REPORTS

Before operation, six of the eight patients had arterial hypertension and one had diabetes mellitus (table I). The indication for Caesarean section was fetal distress in two patients and general anaesthesia was administered. Extradural analgesia was used for three of the remaining six patients and of these one (no. 7) is presented in detail because of the development of persistent hypotension associated with cephalad retraction of the panniculus during operation. General anaesthesia (thiopentone 3 mg kg^{-1}, 0.5% halothane and 40% nitrous oxide) was used for five patients and, of these, two became hypertensive during intubation of the trachea (table I, patients nos 2 and 4). In patient 4, acute pulmonary oedema followed removal of the tracheal tube. The course after anaesthesia was uneventful in six patients. One suffered pulmonary oedema and one minor wound sepsis.

Patient no. 4

A 31-yr-old parturient (weight 163 kg, height 155 cm) had not attended an antenatal clinic and was admitted because of extreme confusion and incoherent behaviour and speech. Almost immediately there was a convulsion but no evidence of pulmonary aspiration. The arterial pressure was 170/120 mm Hg and proteinuria was noted. Magnesium sulphate 4 g i.v. and 10 g i.m. was administered with hydralazine 5 mg i.v. There was evidence of fetal distress

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0007-0912/80/090919-05 $01.00

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TABLE I. *Details of eight grossly obese patients undergoing Caesarean section*

	Patient							
	1	2	3	4	5	6	7	8
Age (yr)	26	28	23	26	26	19	43	27
Height (cm)	155	155	173	155	152	177	152	163
Weight (kg)	159	150	177	163	156	163	204	151.5
Parity	2	3	0	3	0	0	0	1
Apgar score, 1/5 min	9/9	5/7	5/8	2/6, 3/8	7/9	0/3	0/0	1/5
Weight of baby (g)	3686	4137	5657	1531, 2000	3204	3289	1658	3544
Incision to delivery (min)	7	9	7	19	8	7	45	30
Anaesthesia	Extradural (to T4)	General	General	General	Extradural (to T4)	General	Extradural (to T4)	General
Complications								
Before anaesthesia	Asthma Hypertension	Diabetes Hypertension	Hypertension	Prolapsed cord Fetal distress	Rheumatic fever Hypertension	Prolapsed cord Fetal distress	Hypertension	Asthma Hypertension
During anaesthesia	None	AP increased during intubation	None	AP increased during intubation	None	None	AP decreased Respiratory difficulty	None
After anaesthesia	None	Minor wound infection	None	Pulmonary oedema	None	None	Abdominal dehiscence	None

and Caesarean section was performed; general anaesthesia comprised thiopentone, nitrous oxide, oxygen and halothane and 0.2% suxamethonium infusion.

The arterial pressure increased from 170/120 to 270/160mm Hg during tracheal intubation. Hydralazine 5 mg was given i.v. The arterial pressure gradually decreased to 140/80 mm Hg after 45 min of anaesthesia. Undiagnosed twins were delivered after 19 min of surgery. Oxytocin 20 units was given i.v. Fifteen minutes after the completion of surgery, the patient developed acute dyspnoea and a respiratory frequency of 44 b.p.m. The arterial pressure was 126/50 mm Hg and the heart rate 104 beat min^{-1}. Auscultation of the lungs revealed rales throughout both lower lobes. Pa_{O_2} was 8.8 kPa, Pa_{CO_2} 4.5 kPa and pH 7.35 (breathing air). The central venous pressure was 14–18 mm Hg. The differential diagnosis lay between pulmonary oedema following left-sided heart failure and Mendelson's Syndrome following silent aspiration during the preoperative convulsion. Chest x-ray and e.c.g. were normal. Frusemide 60 mg and digoxin 0.7 mg were administered i.v. followed by digoxin 0.25 mg i.v. three times at 6-h intervals. There was a marked diuresis and no further attacks of dyspnoea. Arterial blood analysis was repeated 45 min later when Pa_{O_2} was 12 kPa, Pa_{CO_2} 3 kPa and pH 7.40 (room air). The patient was given oral digoxin 0.125 mg daily and methyldopa 500 mg four times daily. She was discharged from hospital on the 10th day after operation when the arterial pressure was 120/70–130/80 mm Hg.

Patient no. 7

A 43-year-old woman (weight 204 kg, height 152 cm) was admitted complaining of lower abdominal pain. There was a 34-week history of amenorrhoea and she had been investigated at a fertility–endocrine clinic. Vaginal examination and ultrasound were unhelpful because of obesity but x-ray revealed a single fetus compatible with 34 weeks gestation. This primigravida underwent Caesarean section as there had been little progress during 15 h labour. Hypertension (arterial pressure 160/110 mm Hg) was noted before the pregnancy. Extradural block was performed, producing sensory loss to T4. The operation was unavoidably delayed for 45 min during which time the arterial pressure was stable at 130/90 mm Hg. An attempt to retract the panniculus cephalad by strapping it to the anaesthesia screen resulted in a decrease in arterial pressure to 100/60 mm Hg and manual retraction by two assistants was substituted. A Pfannenstiel incision was made and 15 min later the arterial pressure decreased to 100/70 mm Hg and after 25 min to 80/60 mm Hg. The pressure returned to 130/90 mm Hg when retraction was reduced. A dead baby weighing 1900 g was delivered after 45 min. In order to suture the uterus, retraction had to be increased and the patient had difficulty breathing. The trachea was intubated 55 min after the operation commenced and removal of the tracheal tube was possible 75 min later (the patient remained awake throughout the procedure). The Caesarean section was completed in 126 min when the arterial pressure was 112/60 mm Hg and the heart rate 120 beat min^{-1}. The estimated blood loss was 1200 ml. Pa_{O_2} was 13.3 kPa, Pa_{CO_2} 4.3 kPa (room air) in the recovery room. The post-partum course was uneventful apart from a wound dehiscence extending to the abdominal fascia. The wound healed by granulation. No endocrine cause was found for the massive obesity and the patient was discharged on the 27th day after operation. Panniculectomy was planned by the plastic surgery unit.

DISCUSSION

There are three methods by which a panniculus can be retracted, all being associated with varying adverse effects on cardiovascular and respiratory function. Caudal retraction permits a vertical incision (fig. 1A). A vertical incision above the panniculus also allows other abdominal wall adipose tissue to be retracted laterally rather than cephalad. A Pfannenstiel incision can be performed following cephalad retraction as recommended by Ahern and Goodlin (1978) (fig. 1B) and, theoretically, following vertical retraction by skewers inserted through the abdominal skin (fig. 1C). The Pfannenstiel incision has the advantage that the thickness of adipose tissue above the pubis is minimal, abdominal closure is more secure since wound approximation is likely when the patient coughs, and hypoxaemia after operation is less (Vaughan and Wise, 1975). However, it has been associated with a longer operating time, greater blood loss and poorer exposure (Morrow et al., 1977). As in patient no. 7, a more important objection to this method is the obstruction to the vena cava by a weight equivalent to that of a normal size adult added to the upper abdomen.

Dyspnoea may occur during extradural anaesthesia or excessive airway pressure may be needed during general anaesthesia when the panniculus is retracted (especially cephalad). Total respiratory compliance is reduced in obesity because of the effects of a heavy chest wall and increased abdominal pressure. The work of breathing is increased. Reduced compliance is associated with a low residual volume and functional residual capacity. Functional residual capacity is not only decreased by obesity but also by pregnancy (Hytten and Lind, 1973), the supine position (LeBlanc, Ruff and Milic-Emili, 1970) and general anaesthesia (Rehder, Sessler and Marsh, 1975). The reduction of functional residual capacity by general anaesthesia is maintained in the period after operation (Alexander et al., 1973). One-third of pregnant patients have been shown to develop airway closure during normal tidal volumes in the supine position (Bevan, 1974). The airways in the dependent lung are the most likely to close and such closure will lead to distribution of pulmonary blood flow to underventilated areas producing a shunt and causing a reduction in arterial oxygen tension. The respiratory difficulties inherent in anaesthesia for the obese parturient in the supine position were compounded in patient no. 7 by the necessity for extreme retraction to permit closure of the Pfannenstiel incision.

Gross obesity is associated with hypertension, increased cardiac output, limited cardiac reserve (Fisher, Waterhouse and Adams, 1975) and, in the parturient, with pre-eclampsia. More than 50% of deaths associated with pre-eclampsia are a result of

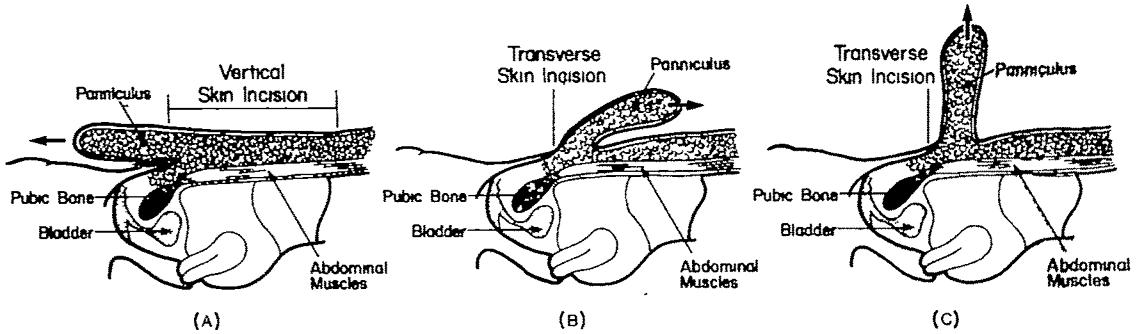

FIG. 1. The panniculus is shown (A) retracted caudad to permit a vertical incision above; (B) retracted cephalad to permit a transverse Pfannenstiel incision and (C) retracted vertically. Direction of retraction is shown by arrows.

cerebral haemorrhage and approximately another 10% a result of cardiac failure (Arthure et al., 1975). During tracheal intubation, patient no. 2 developed an increase in arterial pressure from 140/80 to 230/110 mm Hg and patient no. 4 from 190/110 to 270/170 mm Hg. All pressures were measured by auscultation. In patient no. 4 pulmonary oedema developed shortly after the tracheal tube was removed, probably because of left ventricular failure secondary to the effects of marked increases in afterload.

Grossly obese patients have larger volumes of gastric fluid and more gastric acidity than the non-obese (Vaughan, Bauer and Wise, 1975). These patients, especially, should be considered to be at risk from acid aspiration and should be treated with antacids before induction of either regional or general anaesthesia.

The incision–delivery time is increased by surgical difficulties and marked retraction may interfere with uterine blood flow without decreasing arterial pressure. It is preferable, therefore, to monitor the fetal heart rate during the operation. A decrease in fetal heart rate could constitute an indication for intermittent retraction. In patient no. 8, the fetal heart rate decreased from 140 to 70 beat min^{-1} following incision of the uterus and remained at 70 beat min^{-1} during the 3 min needed to extract the baby; the Apgar score was 1 at 1 min and 5 at 5 min.

Extradural analgesia was chosen for three patients (nos 1, 5 and 7). In patient 7, the critical reduction in arterial pressure was not a result of the extradural block *per se* since the pressure was stable and remained greater than 130/90 mm Hg for the 45 min before surgery and returned to the same value whenever retraction was reduced. Provided that the patient has not received narcotics, is given a crystalloid infusion rapidly through two large-gauge i.v. needles, and that her uterus is displaced laterally, the frequency of hypotension (< 100 mm Hg systolic) was 18 of 147 Caesarean sections (12%), ephedrine being used in three (2%) (Hodgkinson and Husain, 1980).

Extradural analgesia offers considerable advantages in the presence of gross obesity. Its use in intestinal short-circuiting procedures for massive obesity has been advocated by Fox (1975) and Bromage and Fox (1976). The successful use of extradural analgesia for Caesarean section in a parturient weighing 182 kg has been reported by Maitra and others (1979). The risk of Mendelson's Syndrome is reduced, the episodes of extreme hypertension during intubation of the trachea and removal of a tracheal tube are avoided and 100% oxygen can be administered. Adequate time can be allowed for surgery without exposing the fetus to the continued transfer of thiopentone, nitrous oxide and halothane and without loading the maternal adipose tissues with these agents and their metabolites (Young, Stoelting and Peterson, 1975) which may be recycled to the neonate during breast feeding. Analgesia can be continued into the period after operation, permitting deep breathing without the use of narcotics, and early movement of the legs in an attempt to prevent thromboembolism, the commonest cause of mortality after surgery. The disadvantage of hypotension can be minimized by the rapid infusion of crystalloid fluids, and by uterine displacement to the left. However, small-dose heparinization before operation to prevent thromboembolism is considered by us a contraindication to extradural block.

We do not consider a Pfannenstiel incision to be justified. Additional time is needed to deliver the baby. If it is used, some method of retracting the panniculus vertically should be devised. Cephalad retraction can result in formidable cardiovascular and respiratory problems dangerous to both mother and baby. A longer than normal vertical incision would permit rapid delivery of the baby and reduce cardiovascular and respiratory embarrassment by allowing both lateral and caudal retraction of adipose tissue.

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OPERATION CESARIENNE ASSOCIEE A UNE TRES FORTE OBESITE

RESUME

On décrit dans cet article les problèmes d'anesthésie et les problèmes chirurgicaux rencontrés lors d'opérations césariennes effectuées sur 8 femmes extrêmement obèses (pesant entre 150 et 204 kg). En plus d'une augmentation dans la fréquence et l'importance des complications de l'obésité, celles pesant plus de 150 kg présentaient un pannicule adipeux pesant jusqu'à 70 kg. On a utilisé l'analgésie extradurale pour trois patientes et l'anesthésie générale pour les cinq autres (deux à cause de la détresse du foetus). L'un des foetus est mort *in utero*, après une grave hypotension artérielle prolongée chez la mère, causée par la puissante rétraction céphalique du pannicule (analgésie extradurale). L'anesthésie générale a été associée à de sévères épisodes d'hypertension chez deux patientes.

KAISERSCHNITT IM ZUSAMMENHANG MIT STARKER FETTLEIBIGKEIT

ZUSAMMENFASSUNG

Die Narkose- und Chirurgieprobleme bei Kaiserschnitten an acht stark fettleibigen Patientinnen (Gewicht 150 bis 204 kg) werden beschrieben. Zusätzlich zur erhöhten Häufigkeit und Schwere der Komplikationen durch Fettleibigkeit, zeigen Patientinnen über 150 kg einen Panniculus, der 70 kg wiegen kann. Extraduralanalgesie wurde bei drei, und allgemeine Narkose bei fünf Patientinnen (2 davon wegen Fotus-Notstand) gegeben. Ein Fötus starb *in utero* nach schwerer und langer arterieller Hypotension in der Mutter, bewirkt durch starke Kopfretraktion des Panniculus nach extraduraler Analgesie. Allgemeine Narkose bewirkte bei 2 Patientinnen schwere Anfälle von Hypertension.

EL CORTE DE CESAREA EN RELACION CON LA OBESIDAD EXCESIVA

SUMARIO

Se describen los problemas anestésicos y quirúrgicos asociados con el corte de cesarea en 8 pacientes excesivamente gruesas (pesos de 150 a 204 kg). Además de un incremento en la frecuencia y gravedad de las complicaciones que conlleva la obesidad, aquellas con un peso superior a 150 kg presentaron un paniculus que puede pesar 70 kg. Se usó analgesia extradural en tres pacientes y anestesia general en cinco de ellos (en dos a causa del malestar del feto). Un feto murió *in utero* después de que la madre sufriera una seria y prolongada hipotensión arterial, causada por una poderosa contracción cefálica del paniculus (analgesia extradural). La anestesia general vino asociada con graves etapas de hipertensión en dos de las pacientes.

Br. J. Anaesth. (1980), **52**, 925

EFFICIENCY OF TWO VARIABLE PERFORMANCE TECHNIQUES OF OXYGEN THERAPY IN RELIEVING POSTOPERATIVE HYPOXAEMIA

J. B. JACOBSEN, H. NIELSEN, M. M. BRINKLØV, D. B. STOKKE AND J. F. HARTMANN-ANDERSEN

SUMMARY

The efficiency of two patient-dependent, variable performance techniques of oxygen therapy in relieving hypoxaemia after upper abdominal surgery was compared. A high-flow system delivered a humidified mixture of oxygen 2 litre min^{-1} and air 13 litre min^{-1} through a cannula inserted into the anterior nares. The low-flow system delivered 2 litre min^{-1} of dry oxygen into the nasopharynx through a catheter. Thirteen otherwise healthy patients received either high-flow oxygen therapy for 30 min followed by low-flow oxygen therapy for a further 30 min after operation or the same therapy in reverse order. With the patients breathing room air, arterial hypoxaemia could be demonstrated with Pa_{O_2} inversely related to age. The increase of Pa_{O_2} during either oxygen treatment was significantly greater with the low flow system.

Impairment of arterial oxygenation in the period after operation is a common occurrence even in young patients without pre-existing respiratory or cardiovascular disease. The impairment is most profound and persistent after upper abdominal surgery and thoracotomy. However, arterial hypoxaemia seems an almost inevitable sequel to surgery requiring general anaesthesia for more than 20 min, despite normal Pa_{CO_2}, cardiac output and oxygen consumption, and in absence of evident pulmonary complications. Extensive reviews on the subject have been presented (Sellery, 1968; Marshall and Wyche, 1972; Conway, 1975; Hewlett and Branthwaite, 1975).

Although the beneficial effect of oxygen therapy in relieving hypoxaemia after operation has been well established, there are relatively few controlled clinical trials which have assessed the comparative efficiency of techniques available for the administration of oxygen (Conway and Payne, 1963; Heller, Watson and Imredy, 1965; Robertson, 1969; Tantum, 1969; Drummond, 1975; Drummond and Milne, 1977; Drummond and Wright, 1977). We have compared two commonly used, patient-dependent, variable performance devices applying a high-flow, humidified, and a low-flow, dry oxygen delivery technique, respectively.

PATIENTS AND METHODS

Thirteen adult patients (table I) with no symptoms or signs of chest or heart disease, who had undergone upper abdominal surgery were studied. All had received diazepam orally about 1 h before operation. Anaesthesia was induced with thiopentone and suxamethonium was given to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide in oxygen and either halothane or droperidol and fentanyl. Neuromuscular blockade was produced with pancuronium and antagonized at the end of the operation with neostigmine and atropine. With the patient breathing spontaneously, pure oxygen was administered for the 7 min before withdrawal of the tracheal tube. The patients were allocated randomly to receive either high-flow, humidified oxygen therapy for 30 min followed by low-flow, dry oxygen therapy for a further 30 min or the same in reverse order.

In the recovery room femoral artery blood was sampled and the time noted. A second sample was taken after 30 min of oxygen treatment and a third at the end of the second treatment. Samples were collected in heparinized 1-ml B 109 Arterial Blood Sampler Syringes (Radiometer) and were analysed for P_{O_2}, P_{CO_2} and pH at 37 °C within 3 min of collection using an automatically calibrated ABL-2 Acid–Base Laboratory (Radiometer) with a halothane-insensitive E5049 oxygen electrode (Kokholm and Mikkelsen, personal communication). The results were corrected for the difference in temperature between the patient and the electrode (Severinghaus, 1966).

The high-flow system was devised to administer oxygen or oxygen–air mixtures through a nasal

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0007–0912/80/090925–06 $01.00

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cannula at high flow rates approximating to the peak inspiratory flow, thereby decreasing the admixture of room air (Lomholt, 1968). To make this acceptable to the patient the gas must be saturated with water vapour at body temperature. A mixed flow of oxygen 2 litre min^{-1} and atmospheric air 13 litre min^{-1} entered the system from two separate Rotameter flowmeters and passed through a hot water humidifier (Hygrotherm, S & W, Copenhagen) with a temperature of 50–55 °C to achieve full saturation and a temperature close to 37 °C at the patient end of the system. The mixture was delivered to the patient through a 25-cm (i.d. 6 mm) flexible soft plastic tube with the distal 1-cm nylon foam-collared end inserted into the anterior nares and the proximal end connected to the humidifier through a 160-cm wide-bore corrugated tube with a T-piece interposed to allow measurement of temperature.

In the low-flow system oxygen 2 litre min^{-1} was delivered to the patient through a 40-cm (i.d. 2 mm) soft plastic catheter with the distal perforated end placed so that the tip was just visible beneath the soft palate and the proximal end connected to the flowmeter through a 160-cm (i.d. 6 mm) rubber tube. The same flowmeter unit was used for both treatments.

Statistics

Fisher's exact probability test was applied to data with a nominal scale of measurement. Data with a ratio scale of measurement were analysed with the Mann–Whitney test when comparing the data of two random samples and the Wilcoxon test when comparing paired observations. The relationship between Pa_{O_2} and age was assessed by calculation of the least squares linear regression. The level of significance was 0.05.

RESULTS

Six patients received low-flow oxygen therapy followed by high-flow (group A), and seven received the reverse order (group B). There was no disparity in age, sex, weight, height, deviation from the average weight (Documenta Geigy, Scientific Tables) or time lag from extubation to withdrawal of the first arterial sample (table I) between the groups. No patient was obese. There were cigarette smokers in both groups, but none smoked more than 10 cigarettes per day. No patient was hypotensive during the study, and none shivered. All had normal haemoglobin concentrations.

The individual Pa_{O_2} and Pa_{CO_2} values breathing air and during either method of oxygen therapy are given in table II. (To facilitate comparison with previous investigations the gas tensions of figures 1 and 2 are stated in mm Hg and in kPa). In figure 1 the Pa_{O_2} values after operation and breathing air are shown in relation to age. Using a mean regression line from normal healthy subjects based on pooled data (Marshall and Wyche, 1972) as reference the Pa_{O_2} were decreased consistently after operation. A significant negative correlation between Pa_{O_2} and

TABLE I. *Age, sex, weight, height, deviation from average weight, and time lag between extubation and the first arterial blood sample for the two groups of patients*

Patient number	Age (yr)	Sex	Weight (kg)	Height (cm)	% of average weight	Time lag extubation–arterial sample (min)	Surgical procedure
Group A							
1	53	M	88	185	103	20	Cholecystectomy
2	51	F	49	149	86	15	Selective vagotomy
3	61	F	67	158	108	35	Cholecystectomy
4	39	F	65	169	102	40	Cholecystectomy
5	62	F	52	163	79	10	Gastric resection
6	47	M	80	179	100	20	Selective vagotomy
Group B							
7	31	M	58	169	83	20	Selective vagotomy
8	37	F	61	171	93	20	Selective vagotomy
9	30	M	70	179	90	20	Cholecystectomy
10	40	M	95	192	104	15	Cholecystectomy
11	53	F	51	160	80	20	Cholecystectomy
12	41	M	75	185	88	25	Exploratory laparotomy
13	58	F	50	173	69	20	Intestinal resection

TABLE II. *Pa_{O_2} and Pa_{CO_2} values (kPa) after operation, breathing room air and during high-flow and low-flow oxygen therapy. Group A received low-flow therapy followed by high-flow therapy, while in group B the order was reversed*

Patient number	Breathing room air		During oxygen therapy			
			High-flow		Low-flow	
	Pa_{O_2}	Pa_{CO_2}	Pa_{O_2}	Pa_{CO_2}	Pa_{O_2}	Pa_{CO_2}
Group A						
1	9.3	5.5	9.5	5.7	15.8	5.7
2	8.1	6.1	10.2	5.5	10.3	6.2
3	10.2	5.8	11.3	5.8	14.1	6.1
4	11.4	5.1	16.6	5.4	20.1	5.2
5	7.3	7.0	16.0	6.1	23.1	7.0
6	7.3	7.1	12.6	6.5	13.7	7.1
Group B						
7	9.6	8.3	11.8	8.1	14.5	8.3
8	10.0	5.4	12.3	5.0	12.5	5.1
9	11.0	6.3	12.8	6.3	15.8	6.5
10	10.4	5.3	15.1	5.8	16.5	5.4
11	6.6	6.4	11.5	5.8	20.2	5.4
12	8.8	6.2	10.8	6.1	15.2	6.2
13	7.2	4.8	8.0	5.1	12.5	5.1

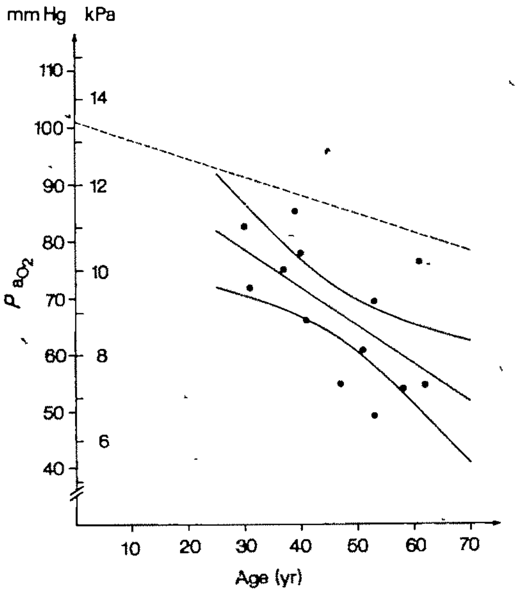

FIG. 1. Pa_{O_2} of 13 patients, breathing room air immediately after upper abdominal surgery, in relation to age. The least squares linear regression line, and the 95% confidence limits for the regression estimate are shown ($r = -0.61$, $P<0.05$; $y = -0.67x+98.6$). The dotted line represents a mean regression line from normal healthy subjects based on pooled data.

age could be shown, and the slope of the calculated regression line was appreciably steeper than that of the mean regression line.

During high-flow oxygen therapy Pa_{O_2} in more than half of the patients exceeded the corresponding value of the mean regression line, while all but one exceeded these values during low-flow therapy. However, no correlation between Pa_{O_2} and age could be demonstrated during oxygen therapy.

The distribution of Pa_{O_2} and Pa_{CO_2} breathing air and during oxygen treatment is shown in figure 2. Both methods of oxygen therapy resulted in statistically significant increases of Pa_{O_2}. However, Pa_{O_2} during low-flow therapy was significantly greater than Pa_{O_2} during high flow. There was no difference between values in group A and group B. Pa_{CO_2} did not change significantly after oxygen therapy, and there was no difference in Pa_{CO_2} between low-flow and high-flow therapy.

DISCUSSION

Oxygen therapy has an effect on arterial oxygenation in the presence of true shunt fractions up to about 30% (Benatar, Hewlett and Nunn, 1973). However, as high oxygen concentrations are required to compensate entirely for even moderate degrees of

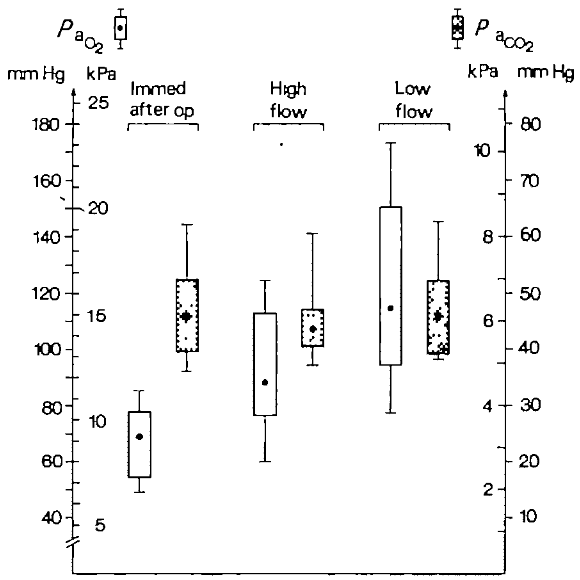

FIG. 2. The distribution of Pa_{O_2} and Pa_{CO_2} during breathing of room air immediately after operation, and during either method of oxygen administration (n = 13). The medians, the 95% confidence limits for the medians and the range of observations are indicated.

shunting, arterial hypoxaemia resulting from an increase in frank shunting cannot be overcome by conventional oxygen therapy, whereas the decrease in Pa_{O_2} in the period after operation is restored usually to normal by even modest oxygen enrichment. There is evidence indicating two separate components of hypoxaemia following surgery (Conway, 1975; Leigh, 1975). Early hypoxaemia occurs in the first few hours after operation, has little relationship to operative site, and is chiefly attributable to mismatching of ventilation to perfusion (Kitamura, Sawa and Ikezono, 1972). Late hypoxaemia depends upon the site of operation, and is the result of the combined effects of ventilation/perfusion imbalance and transpulmonary shunting (Conway, 1975).

Several reports have confirmed that age affects postoperative oxygenation (Palmer and Gardiner, 1964; Marshall and Millar, 1965; Nunn, 1965; Fairley et al., 1968; Davis and Spence, 1972; Drummond, 1975) and that the inverse relation between Pa_{O_2} and age normally seen in healthy conscious man (Conway, Payne and Tomlin, 1965; Marshall and Millar, 1965; Fairley et al., 1968; Kitamura, Sawa and Ikezono, 1972; Drummond, 1975) may be exaggerated (Palmer and Gardiner, 1964; Kitamura, Sawa and Ikezono, 1972; Drummond, 1975).

In the present investigation marked hypoxaemia was encountered in the period immediately after operation. The mean Pa_{O_2} value in this study corresponds closely to those found by Palmer and Gardiner (1964), Kitamura, Sawa and Ikezono (1972), Drummond (1975) and Drummond and Wright (1977) in similar clinical circumstances, but the regression line relating Pa_{O_2} to age was steeper (slope = -0.67 against -0.43, -0.43, -0.47 and -0.48) and the intercept slightly greater (98.6 against 97.7, 94.0, 88.9, and 90.4). This may reflect the short time lag between extubation and measurement of P_{O_2} in this study.

In the period immediately after the termination of anaesthesia "post-hyperventilation hypoxia" (Salvatore, Sullivan and Papper, 1969) and "diffusion hypoxia" (Fink, 1955; Frumin and Edelist, 1969) may contribute to arterial hypoxaemia. However, these effects are transient and mild, and considering the time lag from withdrawal of nitrous oxide and return of spontaneous respiration to the first arterial sample, it is unlikely that they have influenced the results. In one patient (number 7) significant hypercapnia may account for the hypoxaemia observed. Pa_{CO_2} values of the remaining 12 patients were normal or near normal, and did not change significantly during the investigation. The greatest tracheal or alveolar oxygen concentrations achieved by the administration of oxygen at a flow rate of 2 litre min^{-1} through nasopharyngeal catheters or nasal cannulae do not exceed 25% (Bethune and Collis, 1967; Gibson et al., 1976). Even so, Pa_{O_2} increased significantly during both forms of oxygen therapy, strongly supporting the concept of ventilation/perfusion inequality as a factor of major importance in early postoperative hypoxaemia. The great variation of Pa_{O_2} during therapy, and poor correlation with age, probably reflects different respiratory patterns among the patients, as both systems were patient-dependent with flow rates of less than the normal peak inspiratory flow rate. A varying degree of true shunt and maldistribution of ventilation from patient to patient may have contributed to the scatter; and even the effect of controlled oxygen therapy is predicted only poorly on the basis of the age of the patient, suggesting other factors, such as posture, smoking, pain and abdominal distension (Drummond, 1975).

There are two explanations of the different Pa_{O_2} values with high-flow and low-flow therapy. First, the flow rate of the gas delivered to the patient dictates that the gas can be utilized completely only during the part of inspiration where the inspiratory flow rate exceeds the flow rate of the gas. During the rest of the breathing cycle varying amounts of the gas offered will be lost. Obviously, the unexploited fraction of the total flow, and consequently of the oxygen flow, will increase with increasing flow rate. Thus, the high flow rate resulting from the intentional dilution of oxygen with air causes more of the delivered oxygen to be lost than the low flow rate of undiluted oxygen. Second, administration of gas by the nasal route causes a reduction in the effective deadspace resulting from flushing of the nasal and pharyngeal sections of the anatomical deadspace during the last part of expiration and in the post-expiratory pause (Bethune and Collis, 1967; Leigh, 1970; Shapiro, 1973). Low-flow therapy will result in a small anatomical reservoir with high oxygen concentration, while high-flow therapy will produce a greater reservoir with a lower oxygen concentration. As the capacity of the reservoir is limited, the greater oxygen concentration achieved during low-flow therapy may outweigh the greater reservoir during high flow.

Although the oxygen flux is determined by the product of arterial oxygen content and cardiac output, a normal Pa_{O_2} is nevertheless an important prerequisite for maintaining sufficient transport of oxygen with no undue strain on the cardiovascular system. In the period after operation this can only be achieved by administration of oxygen. Naturally, the rational foundation of therapy should be the provision of predictable and consistent inspired oxygen concentrations. However, with due respect to resources and priorities, normal Pa_{O_2} values can be accomplished at moderate flow rates of oxygen with simple and cheap, variable performance devices such as nasal cannulae or nasopharyngeal catheters. While the latter method seems to be more efficient at identical small flow rates of oxygen, the former appears to be more comfortable and convenient to the patient (Kory et al., 1962; Tantum, 1969).

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EFFICACITE DE DEUX TECHNIQUES A PERFORMANCES VARIABLES D'OXYGENOTHERAPIE POUR SOULAGER L'HYPOXEMIE POSTOPERATOIRE

RESUME

On a comparé l'efficacité de techniques à performances variables (dépendant des patients) d'oxygénothérapie pour soulager l'hypoxémie après une intervention chirurgicale à la partie supérieure de l'abdomen. Un système à grand débit a livré un mélange humidifié d'oxygène à raison de 2 litres min^{-1} et d'air à raison de 13 litres min^{-1} à l'aide d'une canule introduite dans les narines antérieures. Le système à faible débit a délivré 2 litres min^{-1} d'oxygène sec dans le rhinopharynx par l'intermédiaire d'un cathéter. Treize patients, qui en dehors de cela étaient en bonne santé, ont reçu soit une oxygénothérapie à grand débit pendant 30 min, suivie d'une oxygénothérapie à faible débit pendant 30 autres minutes, après une intervention chirurgicale, ou la même thérapie mais dans l'ordre inversé. Dans le cas des patients respirant l'air ambiant, on a pu prouver l'hypoxémie artérielle, la Pa_{O_2} étant inversement reliée a l'âge. L'augmentation de la Pa_{O_2} pendant l'un ou l'autre de ces traitements à l'oxygène, a été significativement plus grande avec le système à faible débit.

EFFIZIENZ ZWEIER SAUERSTOFFTHERAPIEMETHODEN MIT VARIABLER LEISTUNG ZUR LINDERUNG POSTOPERATIVER HYPOXÄMIE

ZUSAMMENFASSUNG

Die Effizienz zweier vom Patienten abhängigen Methoden der Sauerstofftherapie mit variablen Leistungen, zur Linderung von Hypoxämie nach Unterleibsoperationen wurde verglichen. Ein System mit starkem Durchfluss lieferte eine befeuchtete Mischung von 2 Liter min^{-1} Sauerstoff und 13 Liter min^{-1} Luft über eine in die vordere Nasenöffnung eingeführte Kanüle. Ein System mit niedrigem Durchfluss lieferte 2 Liter min^{-1} an trockenem Sauerstoff über einen Katheter in den Nasenrachenraum. Dreizehn sonst gesunde Patienten erhielten entweder Sauerstofftherapie mit starkem Durchfluss auf 30 Minuten, gefolgt von niedrigem Durchfluss auf weitere 30 Minuten nach der Operation, oder umgekehrt. Die Patienten atmeten Zimmerluft, wobei arterielle Hypoxämie nachgewiesen werden konnte—mit Pa_{O_2} im umgekehrten Verhältnis zu ihrem Alter. Der Anstieg von Pa_{O_2} während den beiden verschiedenen Sauerstofftherapien war bei dem System mit niedrigem Durchfluss wesentlich stärker.

EFICIENCIA DE DOS TECNICAS VARIABLES DE EJECUCION DE TERAPIA DE OXIGENO PARA ALIVIAR LA HIPOXEMIA POSTOPERATIVA

SUMARIO

Se compararon las eficiencias de dos técnicas de ejecución variable, que están en función de paciente, mediante terapia de oxígeno, para aliviar la hipoxemia después de llevar a cabo cirugía de la parte superior del abdomen. Un sistema de gran flujo entregó una mezcla humidificada de 2 litros min^{-1} de oxígeno y de 13 litros min^{-1} de aire, a través de una cánula insertada en las fosas nasales anteriores. El sistema de poco flujo entregó 2 litros min^{-1} de oxigeno seco en la nasofaringe, a través de un cáteter. Trece paciente, sanos en otros respectos, recibieron bien una terapia de gran flujo de oxígeno por espacio de 30 minutos, seguida por una terapia de bajo flujo de oxígeno por un espacio adicional de otros 30 minutos después de la operación, o esta misma terapia en orden invertido. La hipoxemia arterial podría demostrarse mediante la relación inversa entre Pa_{O_2} y la edad, con los pacientes respirando aire de la habitación. El incremento de Pa_{O_2} durante cualquiera de los tratamientos de oxígeno fue significativamente superior para el sistema de bajo flujo.

Br. J. Anaesth. (1980), **52**, 931

COMPARISON OF HAEMODYNAMIC EFFECTS OF METOCURINE AND PANCURONIUM IN PATIENTS WITH CORONARY ARTERY DISEASE

J. HEINONEN AND YRJÖLÄ

SUMMARY

The haemodynamic effects of large bolus doses of metocurine 0.45 mg kg^{-1} and pancuronium 0.1 mg kg^{-1} were compared in patients with coronary artery disease anaesthetized with diazepam, anileridine and nitrous oxide. Hypotension occurred more frequently after metocurine and was a result of a decrease in systemic vascular resistance. After pancuronium there was no increase in arterial pressure or heart rate, but a small increase in cardiac index. The decrease in heart rate after metocurine was the principal cause of the statistically significant difference in cardiac index between the two groups. Contrary to previous findings, metocurine did not attenuate circulatory responses to tracheal intubation. During surgical stimulation, two of the 10 patients of the pancuronium group developed significant ST segment depression and three patients had a rate–pressure product greater than 12 000 mm Hg beat min^{-1}. However, the difference in rate–pressure product between the groups was not statistically significant.

The myoneural blocking drug metocurine (dimethyltubocurarine) was introduced to clinical practice in 1948, but has not been used widely by anaesthetists. Recent studies have revealed that it has no vagolytic effect at cholinergic receptors in the heart and that its ganglion-blocking and histamine-releasing actions are weak (McCullough et al., 1972; Hughes and Chapple, 1976; Savarese, 1979). Stoelting (1974) and Hughes, Ingram and Payne (1976) have reported minimal circulatory effects in patients without cardiovascular disease.

Hypertension, tachycardia and episodes of hypotension should be avoided during anaesthesia for patients with coronary artery disease (Waller, Kaplan and Jones, 1979). Thus, pancuronium has been considered to be the neuromuscular blocker of choice in patients undergoing cardiac surgery (Harrison, 1972; Branthwaite, 1977). However, increases in heart rate and arterial pressure may occur after its administration (Stoelting, 1972). In this study we report a comparison of the cardiovascular effects of large doses of metocurine and pancuronium in patients with coronary artery disease.

PATIENTS AND METHODS

Twenty patients undergoing elective coronary artery bypass surgery were studied (table I). Patients with congestive heart failure, valvular heart disease or an ejection fraction of less than 0.5 were excluded. The purpose of the study and the procedure were explained to the patients, who gave consent. The interval between the last dose of beta-adrenergic blocking drug and induction of anaesthesia was 36–48 h.

TABLE I. *Preoperative data of the patients. Mean values ± SEM*

	Pancuronium	Metocurine
Sex (M/F)	7/3	7/3
Age (yr)	46.3 ± 2.40	47.9 ± 2.30
Weight (kg)	72.6 ± 3.40	78.9 ± 2.90
Body surface area (m^2)	1.82 ± 0.05	1.91 ± 0.05
Physical working capacity (kpm min^{-1})		
< 300	1	3
300–500	7	6
> 500	2	1
Previous myocardial infarction	6	6
Digoxin	3	4
Beta-adrenergic blocking drug	9	9
Ejection fraction	0.65 ± 0.04	0.67 ± 0.04

Anaesthesia and plan of investigation

On the evening before operation the patients were given one to two tablets, each containing pentobarbitone 100 mg and promethazine 25 mg, and 1 h before arrival at the operating theatre, diazepam

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0007–0912/80/090931–07 $01.00

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0.2 mg kg^{-1} was given orally. On arrival an i.v. infusion of 5% glucose solution was commenced and diazepam 0.1 mg kg^{-1} given i.v. Intravascular catheters were inserted under local anaesthesia (1% lignocaine) and the patient was allowed to rest for a few minutes. Control measurements of cardiac output and intravascular pressures were made and blood samples were obtained for analyses of blood-gas tensions, acid–base balance and haemoglobin concentration while the patient was breathing room air.

Anaesthesia was induced with diazepam 0.3 mg kg^{-1}, followed by anileridine 0.4 mg kg^{-1} (Leritine: Merck, Sharp & Dohme) and thiopentone 1 mg kg^{-1}. The injection rate of diazepam was 5 mg min^{-1} and that of anileridine 10 mg min^{-1}, whereas thiopentone was administered within 1 min (Anileridine is approximately four times as potent as pethidine with minimal cardiovascular effects in unanaesthetized patients (Tuominen, Heinonen and Heikkilä, 1976).) From the start of induction, the patients breathed a mixture of 60% nitrous oxide in oxygen via a facemask and a non-rebreathing valve and, when needed, ventilation was assisted or controlled manually.

After a second series of measurements, one of the test drugs was given in double-blind fashion. Pancuronium (Pavulon, Organon) 0.1 mg kg^{-1} or metocurine (Metubine iodide, Lilly) 0.45 mg kg^{-1} was injected rapidly into a peripheral vein and a third set of measurements was made 5 min after the injection. Thereafter, the larynx and trachea were sprayed with 4% lignocaine 3 ml, endotracheal intubation was performed and the patient's lungs were ventilated using an Engström respirator (model 200). At this stage the fourth set of measurements was made.

Artificial ventilation with a 60% nitrous oxide in oxygen mixture was performed at a frequency of 16 b.p.m. In our experience, ventilation with the minute volume derived from the Engström–Herzog nomogram usually produces hypocapnia and so ventilation was performed with a minute volume 10% smaller than that indicated by the nomogram. After endotracheal intubation a further dose of anileridine was given (1.6 mg kg^{-1}, 10 mg min^{-1}). The degree of neuromuscular block was estimated according to the train-of-four principle, using 2 Hz supramaximal stimulation (Wakeling Instruments Ltd) of the ulnar nerve (Lee, 1975). The aim was to maintain a block of at least 80–90%.

A fifth series of measurements was made immediately before surgery commenced and a sixth after sternotomy.

Techniques of measurement

A Swan–Ganz flow-directed thermodilution catheter size 7 F (Edwards Laboratories) was inserted via the right internal jugular vein and its tip was positioned in a branch of the pulmonary artery under pressure and e.c.g. monitoring. This was used for measurement of pulmonary arterial pressure (p.a.p.), pulmonary capillary wedge pressure (p.c.w.p.) and central venous pressure (c.v.p.) and sampling of mixed venous blood. A cannula was inserted to the radial artery for arterial blood sampling and measurement of systemic arterial pressure (AP). The catheters were connected to appropriate transducers and pressures were recorded with an ink-jet recorder (Mingograf 81, Elema–Schönander). The zero reference point was taken as 5 cm posterior to the sternal angle and intravascular pressures were recorded at end-expiration. Leads V_5 and aVF of the e.c.g. were monitored continuously and recorded during the periods of measurement. Cardiac output (CO) was measured using the Swan–Ganz thermodilution catheter and Devices cardiac output computer 3750 (Branthwaite and Bradley, 1968; Aalto-Setälä, Heinonen and Salorinne, 1975).

The blood samples were drawn into heparinized glass syringes and immersed in ice water until analysed. $P\text{O}_2$, pH and $P\text{CO}_2$ were measured and base excess (BE) was derived by an automatic analyser (ABL 1, Radiometer). Corrections for temperature were made, using the nomograms of Kelman and Nunn (1966), if the rectal temperature of the patient was less than 36.5 °C.

Calculations

Systemic vascular resistance (SVR) was calculated as follows:

$$\text{SVR} = \frac{\text{m.a.p.} - \text{c.v.p.}}{\text{CO}}$$

Rate–pressure product (RPP) was calculated by multiplication of the heart rate by systolic arterial pressure; oxygen consumption was derived from CO × arterial–mixed venous oxygen content difference. Blood oxyhaemoglobin saturation was derived from the dissociation curve line charts of Kelman and Nunn (1966).

Statistical analysis

The paired t test was used when the statistical significance of changes within a group was analysed. This test was applied only when the immediate haemodynamic effects of the neuromuscular blocking drugs were studied (stage 3 as compared with stage 2).

The *t* test for two independent samples was used for analysis of the statistical significance between the changes within the two groups. The difference was considered significant when $P \leqslant 0.05$.

RESULTS

Before induction of anaesthesia (stage 1) there was a statistically significant difference in stroke index (SI) and SVR between the two groups (table II). These differences disappeared after induction (stage 2) when a significant difference in c.v.p. was noted.

TABLE II. *Mean systemic arterial pressure (MAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), heart rate (HR), cardiac index (CI), stroke index (SI), systemic vascular resistance (SVR) and rate–pressure product (RPP) during stage 1 (awake) and stage 2 (asleep). Mean values ± SEM.* *P≤0.05; **P<0.01; ***P<0.001 = *significant difference between the two groups*

	1 Awake	2 Asleep
MAP (mm Hg)		
Pancuronium	91±2.1	84±4.3
Metocurine	86±3.5	78±3.9
MPAP (mm Hg)		
Pancuronium	9.4±0.7	14.2±1.4
Metocurine	10.3±1.0	16.1±1.4
PCWP (mm Hg)		
Pancuronium	3.9±0.9	7.8±0.9
Metocurine	1.9±0.5	9.8±1.5
CVP (mm Hg)		
Pancuronium	2.2±0.5	6.8±1.0
Metocurine	2.6±0.9	9.9±1.3***
HR (beat min^{-1})		
Pancuronium	72±2.1	70±3.5
Metocurine	71±3.2	72±5.4
CI (litre m^{-2})		
Pancuronium	2.88±0.16	2.32±0.10
Metocurine	3.28±0.17	2.37±0.14
SI (ml m^{-2})		
Pancuronium	40±2.0	34±2.2
Metocurine	47±2.3*	34±2.4
SVR (unit)		
Pancuronium	18±1.0	19±1.0
Metocurine	13±0.5**	16±1.4
RPP (mm Hg beat min^{-1})		
Pancuronium	9816±360	8326±722
Metocurine	9070±688	7928±805

Figure 1 shows the changes from the haemodynamic values after induction in stages 3–6 of the study. After metocurine (stage 3), there was a significant decrease in m.a.p., m.p.a.p., p.c.w.p., c.v.p., RPP ($P<0.01$), HR and SVR ($P<0.05$). The decrease in m.a.p. can be attributed to the decrease in SVR. After pancuronium, a small but statistically significant increase in CI ($P<0.05$) was found and the small decreases in m.p.a.p., p.c.w.p. ($P<0.05$) and c.v.p. ($P<0.01$) were also statistically significant. When the differences between the changes within the two groups were analysed, the only significant difference was that in CI ($P<0.05$). The decrease in HR in the metocurine group was the principal cause of this difference.

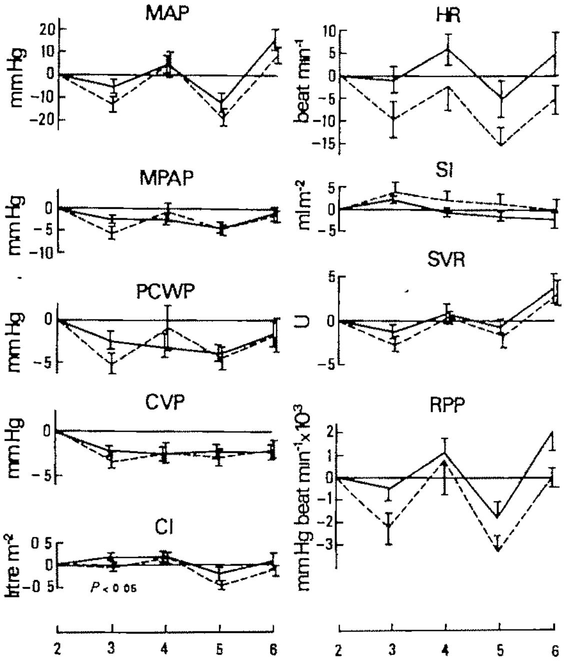

FIG. 1. Mean changes from the postinduction values of mean systemic arterial pressure (MAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), cardiac index (CI), heart rate (HR), stroke index (SI), systemic vascular resistance (SVR) and rate–pressure product (RPP) after: induction (2), relaxant (3), intubation (4); and before and after sternotomy (5 and 6). The *P* value indicates the statistical significance of the difference between the changes within the two groups. Pancuronium: ——; metocurine: - - -.

In stage 3, a decrease in arterial systolic pressure (s.a.p.) exceeding 30% of the initial (stage 1) value was found in five patients receiving metocurine compared with only one receiving pancuronium. Two minutes after the administration of metocurine in two patients s.a.p. was less than 85 mm Hg (70 and 75 mm Hg, respectively).

After tracheal intubation (stage 4) AP, HR, SVR and RPP increased in both groups. No significant differences between the changes within the two groups occurred (stage 4 as compared with stage 2). An increase in s.a.p. exceeding 30% of the initial (stage 1) value was found only in one patient, who had received metocurine. AP and HR of stage 4 shown in figure 1 are those obtained at the time of cardiac output measurement, after the commencement of automatic ventilation. However, most patients exhibited greater values of AP and HR at the time of tracheal intubation. At the time of greatest s.a.p., the mean increases in RPP from the initial (stage 1) values were 14.5% in the pancuronium group and 17.1% in the metocurine group. No difficulties were encountered in intubating the patients and no additional neuromuscular blocking drug was required during the later period of the study.

In stage 5 (before sternotomy) AP, CI, HR and RPP reached the smallest values. There were no significant differences between the changes within the two groups. A decrease in s.a.p. exceeding 30% of the initial value occurred in five patients of the pancuronium group and in eight of the metocurine group.

Surgical stimulation produced an increase in AP, HR, SVR and RPP, but there were no significant differences between the changes within the two groups (stage 6 compared with stage 2). One patient treated with pancuronium showed an increase in s.a.p. exceeding 30% of the initial value and three patients of the pancuronium group had RPP greater than 12 000 mm Hg beat min^{-1}, whereas the greatest individual RPP value in the metocurine group was 11 200 mm Hg beat min^{-1}.

Significant depression (>0.1 mV) of the ST segment (precordial lead) was found after intubation in one patient given metocurine and after sternotomy in two patients given pancuronium. No significant differences in blood-gas tensions or acid–base indices were found between the groups (table III). Data for calculation of oxygen consumption were obtained in stages 1 and 5 of the study. In stage 5 oxygen consumption was decreased 24 ± 4 ml min^{-1} m^{-2} in the pancuronium group and 34 ± 6 ml min^{-1} m^{-2} in the metocurine group.

DISCUSSION

Design of the study

In most of the previous studies of the haemodynamic effects of metocurine, no comparison has been made with other neuromuscular blocking agents. Furthermore, haemodynamic measurements have generally been made during a steady state as suggested by Kennedy and Kelman (1970). Therefore, we compared haemodynamic measurements after the administration of equipotent doses (Savarese, Ali and Antonio, 1977) of metocurine and pancuronium throughout the course of anaesthesia until surgery had started.

Although our patient groups were comparable in other respects, there were some differences in the initial haemodynamic values which decreased after the induction of anaesthesia. Therefore, we used the post-induction values as control when the haemodynamic effects of the neuromuscular blocking drugs were compared.

Metocurine

The changes found 5 min after the administration of metocurine differ from those reported by Zaidan and colleagues (1977) in patients with coronary artery disease. Their patients showed no decrease in AP or HR, whereas CO increased significantly. These effects may be a result of light anaesthesia (morphine

TABLE III. *Blood-gas tensions and base excess (BE). Mean values ± SEM*

	1 Awake	3 After relaxant	4 After intubation	5 Before incision	6 After sternotomy
Pa_{O_2} (kPa)					
Pancuronium	10.2 ± 0.4	20.5 ± 1.6	20.9 ± 2.4	15.9 ± 1.6	16.4 ± 1.5
Metocurine	10.3 ± 0.5	20.8 ± 1.4	21.3 ± 1.7	16.5 ± 1.3	17.5 ± 1.2
Pa_{CO_2} (kPa)					
Pancuronium	5.0 ± 0.1	5.4 ± 0.2	5.5 ± 0.1	4.5 ± 0.1	4.6 ± 0.1
Metocurine	5.0 ± 0.1	5.1 ± 0.3	5.5 ± 0.2	4.5 ± 0.2	4.7 ± 0.2
BE (mmol litre^{-1})					
Pancuronium	−0.2 ± 0.4	−1.3 ± 0.5	−1.2 ± 0.4	−1.0 ± 0.5	−0.8 ± 0.5
Metocurine	0.0 ± 0.3	−1.6 ± 0.4	−1.6 ± 0.3	−1.0 ± 0.3	−1.2 ± 0.3

$0.5\ \mathrm{mg\ kg^{-1}}$ and 50% nitrous oxide) or the smaller dose ($0.35\ \mathrm{mg\ kg^{-1}}$) and slower rate of injection of metocurine in Zaidan's study.

A small decrease in AP and no change in CI have been reported after metocurine in patients without cardiovascular disease receiving halothane (Stoelting, 1974) or enflurane (Stanley, 1978). During thiopentone–nitrous oxide–i.v. analgesic anaesthesia, metocurine $0.2–0.3\ \mathrm{mg\ kg^{-1}}$ did not produce significant changes in AP or HR (Hughes, Ingram and Payne, 1976; Savarese, Ali and Antonio, 1977), whereas greater doses produced hypotension (Savarese, Ali and Antonio, 1977). Hypotension has been attributed to histamine release and a slow injection rate is recommended when large doses of metocurine are given to patients with poorly compensated circulatory states (Savarese, Ali and Antonio, 1977).

Like Zaidan and others (1977) and Stanley (1978) we observed a small decrease in SVR. Fogdall and DeMaster (1977) have presented evidence to suggest that metocurine may cause venodilatation. Since the filling pressures of the heart were decreased in our patients after metocurine, it is possible that a more rapid infusion of salt solution had partially prevented hypotension. The decreases in filling pressures were not, however, significantly greater after metocurine than after pancuronium.

Pancuronium

Several investigators have reported increases in HR, CO and AP after pancuronium during steady-state anaesthesia (Loh, 1970; Kelman and Kennedy, 1971; Stoelting, 1972; Miller et al., 1975). These changes probably result from the vagolytic action of pancuronium at the cholinergic receptors in the heart (Saxena and Bonta, 1970; Hughes and Chapple, 1976) and they are prevented by atropine (Kelman and Kennedy, 1971; Miller et al., 1975).

Although our patients did not receive atropine, they showed no increase in AP and HR after pancuronium. This finding accords with the results of several other studies in which pancuronium was given to patients about to undergo cardiac surgery (Harrison, 1972; Lyons and Clarke, 1972; Clarke and Lyons, 1977; Maunuksela, 1977). In these studies, as in our own, pancuronium was given immediately after induction of anaesthesia. Therefore, it is probable that the measurements were not made during a steady state. Furthermore, the results may have been influenced by cardiac disease and residual effects of digoxin or beta-adrenergic blocking drugs. Whatever the cause of the absence of increase in HR and AP, it is still possible that the differences in HR, CI and AP at stage 3 between our pancuronium and metocurine groups are a result of the vagolytic effect of pancuronium.

Metocurine v. *pancuronium*

Savarese, Ali and Antonio (1977) have suggested that metocurine may be the myoneural blocking drug of choice during the administration of anaesthesia to patients with coronary artery disease. In these patients increases in RPP or episodes of hypotension may precipitate myocardial ischaemia (Waller, Kaplan and Jones, 1979). In our patients hypotension occurred more frequently after metocurine than after pancuronium (stage 3). Although this hypotension was not associated with ischaemic e.c.g. changes, it is potentially dangerous. In spite of the large doses of myoneural blocking drugs used, no attenuation was observed in circulatory response (RPP) to tracheal intubation in the metocurine group as compared with the pancuronium group. This finding seems to differ from that of Basta and Lichtiger (1977), who compared the effects of metocurine and pancuronium on changes in the tension–time index (TTI) evoked by endotracheal intubation in patients with coronary artery disease and anaesthetized with halothane–nitrous oxide. TTI after intubation was significantly greater in their pancuronium group and 18% of the patients given pancuronium showed ST segment depression.

During surgical stimulation, two patients in our pancuronium group developed significant ST segment depression in the precordial lead and RPP was greater in the pancuronium group than in the metocurine group, although the difference was not statistically significant. Further studies are needed to clarify the efficacy of metocurine in attenuating circulatory responses to various stimuli.

In patients with coronary artery disease a large bolus dose of metocurine offered no obvious advantage over pancuronium. After metocurine, hypotension occurred more frequently than after pancuronium and no significant differences were found in circulatory responses to tracheal intubation or surgical stimulation between the metocurine and pancuronium groups. Our patients were under relatively deep anaesthesia achieved with diazepam, anileridine, thiopentone and nitrous oxide and we realize that the haemodynamics after the administration of a neuromuscular blocking drug depend greatly on the *milieu* into which the drug is administered.

ACKNOWLEDGEMENT

Metocurine was kindly provided by Eli Lilly S.A.

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COMPARAISON DES EFFETS HEMODYNAMIQUES DE LA METOCURINE ET DU PANCURONIUM SUR DES PATIENTS SOUFFRANT D'UNE MALADIE DE L'ARTERE CORONAIRE

RESUME

On a comparé sur des patients souffrant d'une maladie de l'artère coronaire et anesthésiés au diazépam, à l'aniléridine et au protoxyde d'azote, les effets hémodynamiques de doses administrées sous forme de grand bol de métocurine (0,45 mg kg^{-1}) et de pancuronium (0,1 mg kg^{-1}). Il s'est produit plus fréquemment de l'hypotension après la métocurine, hypotension qui a résulté de la diminution de la résistance vasculaire systémique. Après l'administration de pancuronium, il n'y a eu aucune augmentation de la pression artérielle ou de la fréquence cardiaque, mais il y a eu une petite augmentation de l'indice cardiaque. La diminution de la fréquence cardiaque, après l'administration de métocurine, a été la principale cause de la différence, significative du point de vue statistique, dans l'indice cardiaque entre les deux groupes. Contrairement aux constatations antérieures, la métocurine n'a pas atténué les réactions circulatoires à l'intubation trachéale. Pendant la stimulation chirurgicale, deux patients sur les 10 du groupe pancuronium, ont manifesté une dépression significative du segment ST et les trois patients ont eu un produit fréquence–pression supérieur à 12 000 mm Hg battements min^{-1}. Quoi qu'il en soit, la différence entre les groupes du produit fréquence–pression n'a eu aucune signification statistique.

VERGLEICH DER HÄMODYNAMISCHEN WIRKUNGEN VON METOCURIN UND PANCURONIUM BEI PATIENTEN MIT KORONARARTERIENERKRÄNKUNG

ZUSAMMENFASSUNG

Die hämodynamischen Wirkungen grosser Dosen von Metocurin (0,45 mg kg^{-1}) und Pancuronium (0,1 mg kg^{-1}) wurden bei gefässkranken Patienten verglichen, die mit Diazepam, Anileridin und Stickoxyd narkotisiert waren. Hypotension trat haufiger auf Metocurin ein, und war Resultat eines Fallens des systemischen Gefasswiderstandes. Nach Pancuronium kam es zu keiner Erhohung von arteriellem Druck oder Pulszahl, dafür aber des Herzindex. Pulszahlabstieg nach Metocurin war der Hauptgrund des Herzindex-Unterschiedes zwischen den beiden Gruppen. Im Gegensatz zu früheren Ergebnissen erhohte Metocurin nicht die Kreislaufreaktionen auf tracheale Intubation. Während chirurgischer Stimulierung entwickelten 2 der 10 Pancuronium-Patienten ST-Segmentunterdrückung, und 3 Patienten zeigten ein Pulszahl-Druckprodukt über 12 000 mm Hg Schläge pro Minute. Der diesbezügliche Unterschied zwischen den beiden Gruppen war jedoch statistisch nicht wesentlich.

COMPARACION DE LOS EFECTOS HEMODINAMICOS DE LA METOCURINA Y DEL PANCURONIUM EN PACIENTES CON ENFERMEDAD DE LA ARTERIA CORONARIA

SUMARIO

Los efectos hemodinámicos de grandes dosis de tipo bolus de metocurina (0,45 mg kg^{-1}) y de pancuronium (0,1 mg kg^{-1}) se compararon en pacientes con enfermedades de la arteria coronaria, anestesiados con diazepam, anileridina y óxido nitroso. La hipotensión tuvo lugar con más frecuencia después de la metocurina y tuvo como resultado una disminución de la resistencia sistémica vascular. Después del pancuronium no hubo incremento alguno en la presión arterial ni en el rítmo cardiaco, pero se presentó un pequeño incremento del índice cardiaco. La disminución del rítmo cardiaco después de la metocurina fue la principal causa de la diferencia estadísticamente significativa en el índice cardiaco entre los dos grupos. En oposición a los resultados previos, la metocurina no atenuó la respuestas circulatorias a la intubación traqueal. Durante la estimulación quirùrgica, dos de los diez pacientes del grupo de pancuronium desarrollaron una depresión significativa del segmento ST y tres de los pacientes presentaron una relación de rítmo–presión superior a 12 000 mm Hg latidos min^{-1}. No obstante, la diferencia entre la relación de rítmo–presión entre los grupos no fue de un significado estadístico.

Br. J. Anaesth. (1980), **52**, 939

EXPERIMENTAL COMPARISON OF EXTRADURAL AND I.M. MORPHINE

T. A. TORDA, D. A. PYBUS, H. LIBERMAN, M. CLARK AND M. CRAWFORD

SUMMARY

Morphine sulphate 3 or 4 mg was administered to the extradural space in five volunteers. Morphine 10 or 15 mg i.m. was given as control. Extradural administration resulted in an increase of pain threshold in the legs but not in the forehead. There was no significant depression of carbon dioxide response or deterioration of co-ordination or short-term memory. I.m. morphine caused an increase in forehead pain threshold, depression of the carbon dioxide response and some deterioration of cerebral function. Extradural morphine caused urinary retention in four and inability to ejaculate in three of the subjects. The principal site of action of extradural morphine appears to be regional, at spinal cord level, but it appears that autonomic function as well as pain perception can be affected.

Since Behar and others (1979) demonstrated the effectiveness of extradural morphine in relieving severe pain, we have used the technique in more than 80 patients. The majority had pain following thoracic or abdominal operations, but patients with pain from ischaemic legs, abdominal malignancy, trauma, acute and chronic pancreatitis and post-herpetic neuralgia also received relief by this technique. Whenever we changed from intermittent i.m. administration of a narcotic to extradural morphine, the patient reported improved pain relief. Despite reports of respiratory depression following extradural pethidine 50 or 100 mg (Scott and McClure, 1979), morphine 3 or 4 mg appeared to be almost devoid of side-effects in our patients. Arterial pressure was virtually unchanged, the patient could walk if permitted and the sensorium appeared unclouded.

We examined these impressions under controlled conditions by administering morphine 3 or 4 mg extradurally to five volunteers and comparing the effect against that of morphine i.m.

METHODS

The subjects were colleagues and were in good health (table I).

Morphine sulphate used for extradural administration contained sodium metabisulphite as preservative. The morphine sulphate 10 mg in 1 ml was diluted to 10 ml in normal saline, 3 or 4 ml of this solution was further diluted to 10 ml, which was administered in the L3–4 interspace with the subject sitting.

TABLE I. *Details of the five subjects*

Subject	Age (yr)	Sex	Weight (kg)	Dose of morphine (mg) Extradural	Dose of morphine (mg) I.m.
1	34	M	74	4	15
2	45	M	72	4	15
3	30	M	78	4	15
4	35	F	47	3	10
5	29	M	70	4	15

Tests were performed before the injection and from 60 min thereafter. The tests took about 30 min to complete and are recorded in the tables at "75 min" after drug administration. Carbon dioxide response and the pain threshold determinations (see below) were repeated at 3 h after drug administration. Three days to 1 week later the study was repeated except that each subject received morphine 10 or 15 mg i.m. in place of the extradural dose.

Determinations included carbon dioxide response, pain threshold measurement, hand–eye co-ordination, the ability to walk and short-term memory. Pin-prick, light touch, heat and cold sensations were tested and each subject recorded relevant subjective experiences during or immediately following the study.

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0007–0912/80/090939–05 $01.00

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The carbon dioxide response was determined by a modification of the method of Milledge, Minty and Duncalf (1974), with the apparatus shown in figure 1. The subjects rebreathed oxygen from a 5-litre reservoir bag. Minute volume was measured with a Godart pneumotachograph and recorded continuously on the ordinate of a Brush 500 X–Y plotter. The exhaled carbon dioxide concentration was determined by a Datex CD101 infra-red carbon dioxide analyser the output of which was displayed on the abscissa. The right edge of the tracing thus corresponds to end-tidal carbon dioxide concentration, and the slope of the carbon dioxide response curve was determined at this edge in the portion between $F\mathrm{E}_{\mathrm{CO}_2}$ 0.06 and 0.09 which was substantially linear (fig. 2). The use of this portion of the response curve eliminates the initial integration error of the pneumotachograph and the non-linearity produced by initiating rebreathing with a carbon dioxide-free mixture (Read, 1967).

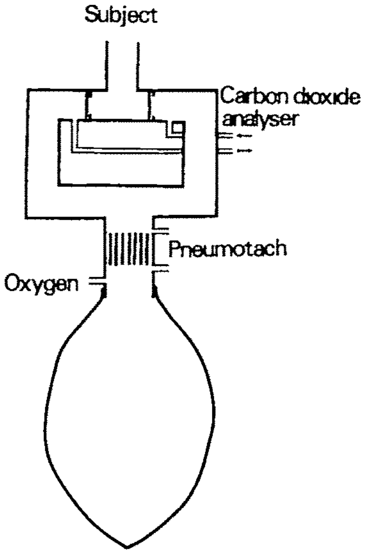

FIG. 1. Diagram of the rebreathing system used to determine the carbon dioxide response.

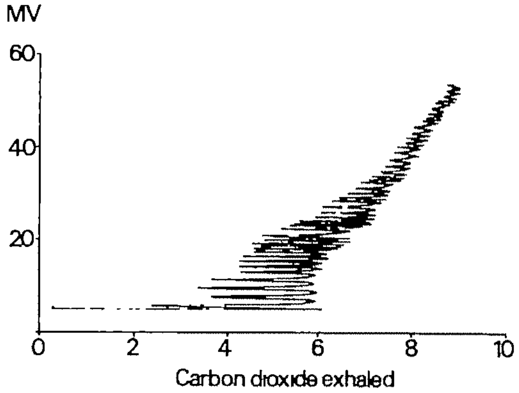

FIG. 2. Control tracing of carbon dioxide response from subject No. 2.

The pain threshold was determined by the method of Clutton-Brock (1957) with a spring balance calibrated in kg using a 4-mm disk. At each determination three readings were taken from each tibia and from the forehead and the average for each site was noted.

Hand–eye co-ordination was tested by a three-dimensional tracking task. Each error caused a buzzer to sound and the number of errors was recorded for each run. The ability to walk was tested by making each subject walk along a marked serpentine line on the floor. Finally, short-term memory was tested by repeating in reverse order five seven-digit numbers, read one at a time to the subject.

At each test session the carbon dioxide response was determined first then the other tests were performed, the arterial pressure and heart rate were recorded and light touch, pin-prick, hot and cold sensation were checked. Finally the carbon dioxide response was determined again.

Statistical significance was tested by single-tailed Student's t test for paired results.

RESULTS

Extradural injection of morphine reduced the carbon dioxide response slightly, but this was not statistically significant at either 75 or 180 min (table II). Following i.m. morphine the depression of carbon dioxide response was significant ($P < 0.05$) at both 75 and 180 min. It is interesting to note that subject No. 2 showed no depression following either the extradural or the i.m. morphine. Following the latter, he was nauseated and vomited repeatedly throughout the study.

Following extradural morphine, pain threshold in the legs was significantly increased after 3 h (table III). There was no effect on the threshold measured on the forehead. After i.m. morphine, however, there was little detectable increase in the pre-tibial threshold, but the increase at the forehead was significant: $P < 0.01$ at 75 min and $P < 0.05$ at 3 h. Readings from the forehead were more consistent in each subject than those from the tibia.

TABLE II. *Effects of extradural and i.m. morphine on carbon dioxide response, litre per min increase per per cent increase in end-tidal carbon dioxide* ($F_{E'_{CO_2}}$ 0.06–0.09). *P < 0.05

	Extradural			I.m.		
	Control	75 min	180 min	Control	75 min	180 min
1	10.7	10.8		10.9	3.7	3.7
2	7.3	8.1	8.2	7.0	7.5	7.5
3	12.5	9.3	9.5	11.8	5.5	6.3
4	3.0	1.5	1.5	5.3	2.5	1.4
5	7.7	5.4	4.8	6.2	3.2	4.7
Mean ± SEM	8.3 ± 1.6	7.0 ± 1.6	6.0 ± 1.6	8.2 ± 1.3	4.5 ± 0.9*	4.7 ± 1.1*

TABLE III. *Pain threshold measurements (arbitrary units) in the legs (L) and head (H) before and after extradural and i.m. morphine* *P < 0.05; **P < 0.01

	Extradural					
	Control		75 min		180 min	
Subject	L	H	L	H	L	H
1	3.7	2.1	3.9	3.0	4.4	2.6
2	2.2	2.1	3.1	2.4	4.4	2.6
3	2.5	2.6	2.1	1.5	2.9	1.3
4	1.0	0.7	1.2	0.7	1.3	1.0
5	2.8	1.5	3.1	1.3	3.4	1.8
Mean ± SEM	2.4 ± 0.4	1.8 ± 0.3	2.7 ± 0.5	1.8 ± 0.4	3.3 ± 0.6*	1.9 ± 0.3
	I.m.					
	Control		75 min		180 min	
Subject	L	H	L	H	L	H
1	3.1	1.7	3.0	2.1	2.9	2.2
2	2.4	1.3	2.3	1.9	2.6	2.0
3	1.6	1.5	1.9	1.7	2.0	2.2
4	0.9	0.7	2.0	1.5	2.3	1.3
5	2.8	1.5	2.9	1.8	2.2	1.4
Mean ± SEM	2.2 ± 0.4	1.3 ± 0.2	2.4 ± 0.2	1.8 ± 0.1**	2.4 ± 0.2	1.8 ± 0.2*

Neither extradural nor i.m. morphine affected the arterial pressure or heart rate significantly. The frequency of tracking errors decreased following extradural morphine; we assume this to be a learning effect. After i.m. morphine it increased. Neither change was statistically significant. Walking errors occurred only after i.m. morphine. The number of errors in the memory task was increased significantly ($P < 0.05$) by i.m. morphine but not by extradural morphine (table IV).

The sensory modalities tested showed little change.

TABLE IV. *Comparison of the results (mean no. of errors, ± SEM) of the tracking, walking and memory tasks before and after morphine administration.* *P < 0.05

Morphine group	Tracking	Walking	Memory
Extradural			
Before	5.0 ± 1.7	0	1.8 ± 0.7
After	1.8 ± 0.6	0	1.4 ± 0.9
I.m.			
Before	2.2 ± 0.8	0	0.8 ± 0.8
After	3.6 ± 1.5	1.2 ± 0.6	1.8 ± 0.7*

One subject reported diminished pin-prick sensation and one diminished heat sensation in the lower half of the body following extradural morphine. No other effects were detected.

A number of other effects was noted. After extradural injection all four male volunteers suffered difficulty in micturition for up to 18 h. Three of the males also had inability to ejaculate and three (not the same three) complained of severe itching in the lower half of the body. Two of the subjects felt slightly euphoric. All subjects appeared able to function normally in other respects.

Following i.m. administration no urogenital side-effects were noted, but three of the subjects were obviously slow in their speech and thought processes and one was nearly incapacitated by nausea and vomiting. Two complained of itching and only one subject appeared to function effectively.

DISCUSSION

Extradural morphine has impressed us by its apparent freedom from side-effects and a long duration of analgesia. This study confirmed these impressions in part only. Respiratory depression caused by extradural morphine 3 or 4 mg was minimal, and the increase in pain threshold in the legs significant. With i.m. administration of morphine the reverse was the case.

In our clinical experience urinary retention has not been a common problem. Of 59 patients who did not have indwelling urinary catheters at the time of receiving extradural morphine analgesia, three had to be catheterized in the next 24 h and a further one reported difficulty in micturition. This contrasts with the four male subjects who could either not pass urine or had slowness in micturition for 12–18 h (although none required catheterization). One possible explanation is that this autonomic disturbance (probably parasympathetic inhibition), is transient and self-limiting in duration, despite continuation of extradural analgesia. The inability to ejaculate despite effective erection, reported by three of the subjects, suggests sympathetic autonomic inhibition as well.

In our clinical experience nausea or vomiting was uncommon. This is borne out by the experience of subject No.2 who tolerated the extradural administration of morphine 4 mg but reacted adversely to 15 mg i.m. The impression of absence of sedation and of cardiovascular effects following extradural morphine was also confirmed.

The mode of analgesic action of extradural narcotics is uncertain. Analgesia by systemic absorption is improbable. Following extradural administration morphine appears about four times as potent and of much longer duration than after i.m. administration. Analgesia is produced with minimal central effects. Alternatively, analgesic action could be achieved through absorption to the cerebrospinal fluid (Cousins et al., 1979) and a central effect; minimal respiratory depression and the absence of detectable effects on psychomotor function, and our finding of an increase in pain threshold in the legs without such an increase on the forehead, suggest that the principal analgesic action is exerted at a spinal level.

The substance P-utilizing synapses of the dorsal horns which are associated with pain pathways (Jessell, 1977; Iversen, 1979) are a likely site, as they are known to be inhibited by opiates and enkephalins. The manner in which the side-effects were caused remains uncertain, but suggests that opiates are less than totally specific to depression of pain pathways in the spinal cord.

ACKNOWLEDGEMENTS

We are indebted to the Division of Respiratory Medicine and Mr P. Owen, their Scientific Officer, for help with setting up of the carbon dioxide response test and for the use of their laboratory. Mr P. de Graaf built the tracking apparatus and Miss Joanne Schubert did our typing with cheerful equanimity. We thank the Department of Medical Illustration for photography of the figures.

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COMPARAISON EXPERIMENTALE ENTRE L'ADMINISTRATION EXTRA-DURALE ET L'INJECTION INTRAMUSCULAIRE DE MORPHINE

RESUME

On a administré une dose de 3 ou 4 mg de sulfate de morphine dans l'espace extra-dural de cinq volontaires. Une dose témoin de 10 ou 15 mg de morphine a été administrée par voie intramusculaire. L'administration extra-durale a accru le seuil de la douleur dans les jambes mais pas dans le front. Il n'y a pas eu de dépression significative dans la réaction au gaz carbonique, ni de détérioration dans la coordination ou dans la mémoire à court terme. L'administration intramusculaire de morphine a accru le seuil de douleur dans le front, la dépression de la réaction du gaz carbonique et une certaine détérioration dans la fonction cérébrale. La morphine extra-durale a provoqué dans quatre cas une rétention d'urine et chez trois des sujets une incapacité d'éjaculer. Le principal site d'action de la morphine administrée par voie extra-durale semble être régional, au niveau de la moelle épinière, mais il semble que la fonction autonome, tout comme la perception de la douleur, peuvent en être affectées.

EXPERIMENTELLER VERLEICH ZWISCHEN EXTRADURAL UND INTRAMUSKULAR VERABREICHTEM MORPHIUM

ZUSAMMENFASSUNG

Morphiumsulphat 3 oder 4 mg wurde extradural an 5 Freiwillige verabreicht. Morphium 10 bis 15 mg wurden intramuskulär als Kontrolle verabreicht. Extradurale Verabreichung führte zu einem Anstieg der Schmerzschwelle in den Beinen, aber nicht in der Stirne. Es kam zu keiner signifikanten Unterdrückung der Kohlendioxydreaktion, und auch zu keiner Verschlechterung des kurzfristigen Gedächtnisses und der Koordination. Intramuskuläres Morphium bewirkte einen Anstieg der Stirnen-Schmerzschwelle, Unterdrückung der Kohlendioxydreaktion und einigen Verschlechterungen der Zerebralfunktionen. Extradurales Morphium bewirkte Harnretention und die Unfähigkeit von Samenerguss bei drei der Freiwilligen. Der Hauptwirkungsort von extradural verabreichtem Morphium scheint regional, auf der Höhe des Rückenmarknervenstranges zu liegen, doch konnen auch die automatische Funktion und die Schmerzerfassung beeinträchtigt sein.

COMPARACION EXPERIMENTAL DE MORFINA EXTRADURAL Y INTRAMUSCULAR

SUMARIO

Se administraron 3 ó 4 mg de sulfato de morfina a la zona extradural de 5 voluntarios. Se administró, a guisa de control, una dosis intramuscular de 10 ó 15 mg de morfina. La administración extradural tuvo como resultado un aumento del dolor umbral en las piernas, pero no en la frente, ni tampoco una deteriorización de la coordinación de la memoria a corto plazo, ni una depresión significativa en la respuesta de dióxido de carbono. La morfina intramuscular tuvo como consecuencia un aumento del dolor umbral en la frente, una depresión en la respuesta de dióxido de carbono y una deteriorización de la función cerebral. La morfina extradural ocasionó retención urinal en 4 de los pacientes e inhabilidad para eyacular en 3. El principal emplazamiento de la acción de la morfina extradural parece ser de caráter regional, a nivel de la espina dorsal, pero parece ser que pueden quedar afectadas la función autonómica y la percepción de dolor.

Br. J. Anaesth. (1980), **52**, 945

PRINZMETAL'S VARIANT ANGINA DURING EXTRADURAL ANAESTHESIA

E. M. KRANTZ, J. F. VILJOEN AND M. S. GILBERT

SUMMARY

A 55-yr-old male undergoing varicose vein surgery with an extradural block complained of chest pain. E.c.g. changes and subsequent examination of the heart including coronary angiography suggested the diagnosis of Prinzmetal's variant angina. The therapeutic implications of this condition in patients undergoing anaesthesia and surgery are discussed.

Continuous monitoring of the e.c.g. during surgical procedures has become the accepted standard of practice. While early detection of arrhythmia remains the primary purpose of such electronic surveillance, deviation of the ST segment from the isoelectric line may be observed. We report a case in which, it is postulated, coronary vasospasm compromised myocardial perfusion and was responsible for the e.c.g. and haemodynamic changes observed.

CASE REPORT

A 55-yr-old black male was admitted to hospital for stripping of varicose veins. Five years before admission he was noted to be mildly hypertensive; this was well controlled with hydrochlorothiazide 50 mg twice daily. On admission arterial pressure was 150/90 mm Hg. The remainder of the physical examination was normal. The patient gave no personal or family history of ischaemic heart disease. The chest x-ray was normal and the electrocardiogram revealed mild left ventricular hypertrophy based on voltage criteria. Renal function was marginal, with the blood urea nitrogen being 2.9 mmol litre^{-1} and the creatinine 141 µmol litre^{-1}; serum sodium was 137 mmol litre^{-1}, potassium 4.5 mmol litre^{-1} and chloride 100 mmol litre^{-1}. The patient was premedicated with pentobarbitone 100 mg and pethidine 50 mg i.m. 1 h before arriving in the operating room. After giving 5% dextrose in lactated Ringer's solution 500 ml i.v., a lumbar extradural block was performed at the L3–4 interspace. Twenty-five millilitre of 1.5% lignocaine with 1 in 200 000 adrenaline was injected to give a block extending to T6. Arterial pressure decreased to 120/70 mm Hg over a 10-min period, and then stabilized. Twenty minutes after the commencement of surgery the patient suddenly complained of retrosternal chest pain. The arterial pressure was 90/60 mm Hg and the electrocardiogram showed elevation of the ST segment, widening of the QRS complex and occasional ventricular premature contractions (fig. 1). Nitroglycerin was given sublingually with immediate relief of pain and return of the ST segment to the baseline (fig. 2). The remainder of the procedure was uneventful. After operation serial electrocardiograms and cardiac enzyme measurements were within normal limits. The patient had no further anginal attacks during his hospital stay.

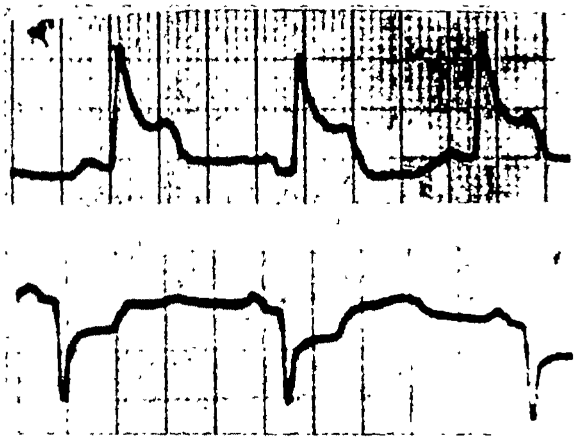

FIG. 1. Leads I and III. ST segment elevation in lead I with reciprocal depression in lead III during acute attack of Prinzmetal's angina.

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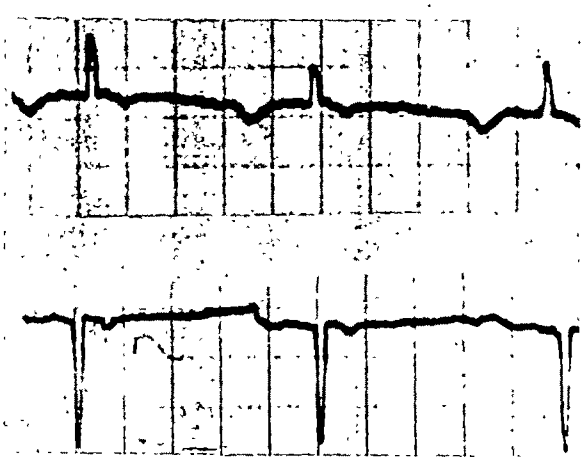

FIG. 2. Leads I and III. Return of ST segments to baseline after nitroglycerin administration.

Following discharge he was referred to the cardiology clinic. A stress electrocardiogram revealed short runs of ventricular tachycardia without deviation of the ST segment.

On cardiac catheterization, left ventricular contraction and haemodynamic function were normal. A coronary angiogram (fig. 3) showed mild narrowing of the left anterior descending and circumflex arteries and a 45% stenosis of the first diagonal branch of the left anterior descending coronary artery; the minimum diameter was 1.2 mm as determined by quantitative angiography (Brown et al., 1977). The same angiographic views were repeated after administration of propranolol 0.2 mg kg^{-1} i.v. (fig. 4) over a 15-min period, followed by three 0.3-mg doses of adrenaline (fig. 5) subcutaneously. The stenosis in the diagonal branch constricted to 0.5 mm (representing a five-fold increase in flow resistance). The circumflex and left anterior descending arteries were virtually unaffected. Nitroglycerin 0.6 mg, given sublingually, dilated the constricted segment to 1.4 mm (fig. 6). The patient did not experience any chest pain during the procedure, despite the severe spasm. This degree of vasoactivity is greater than is usually found in classical angina and a diagnosis of Prinzmetal's or variant angina was made.

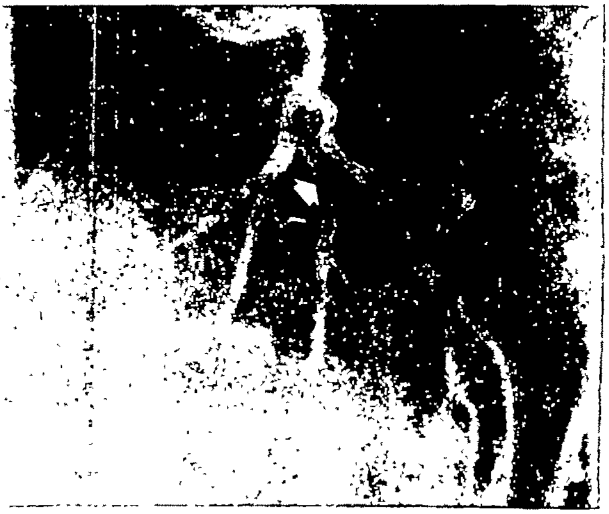

FIG. 4. Coronary vasoconstriction increased after administration of propranolol.

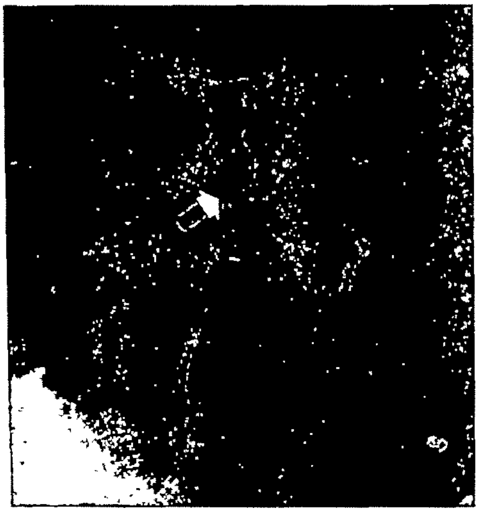

FIG. 3. Coronary angiogram revealing constriction of the first diagonal branch (arrow).

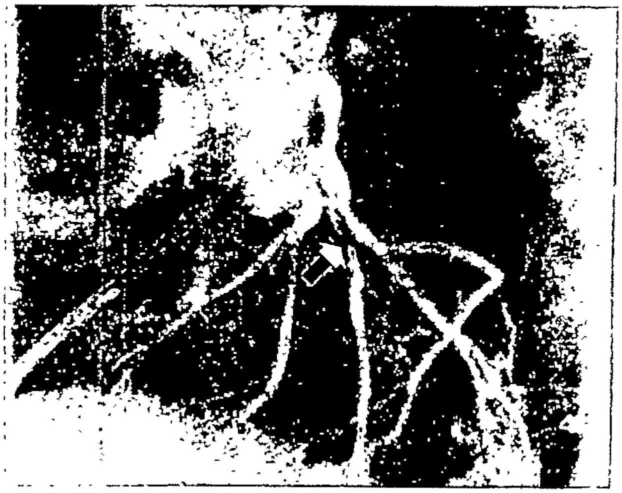

FIG. 5. Severe coronary vasoconstriction after administration of adrenaline.

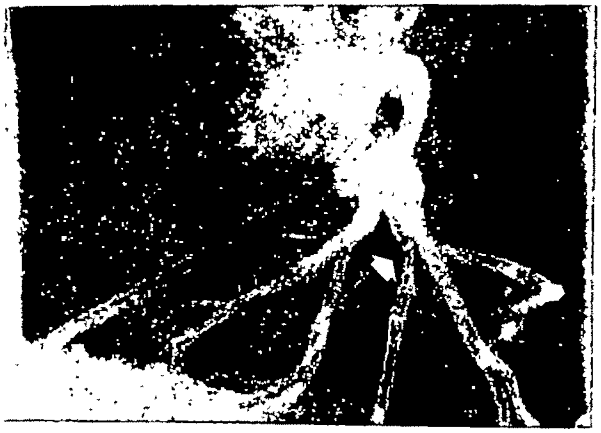

FIG. 6. Vasodilatation following administration of nitroglycerin.

DISCUSSION

In 1959 Prinzmetal and others described 32 patients whose anginal symptoms differed markedly from those of classical angina pectoris. Although the location and character of the pain was similar to classical angina pectoris, it occurred when the patient was at rest or engaged in minimal physical activity. In other words, the pain was not precipitated by any of the factors that are usually associated with increased myocardial oxygen demand.

The electrocardiographic changes during an attack of Prinzmetal's or "variant" angina are diagnostic and consist of ST segment elevation in the lead overlying the ischaemic region associated with ST segment depression in the reciprocal leads. This is in marked contrast to classical angina in which the ST segments are depressed during the attack and reciprocal changes do not occur. The chest pain is promptly relieved by sublingual nitroglycerin and within 1–2 min ST segments return to the baseline. Between the periods of pain the electrocardiogram is normal and the serum transaminase concentrations are unchanged or minimally increased.

The attack of angina in our patient was not preceded by cardiovascular disturbances such as tachycardia, hypertension or severe hypotension. The arterial pressure had stabilized for approximately 20 min following the initial decrease from 150/80 to 120/70 so it is tempting to attribute the chest pain to coronary vasospasm. This in turn would have caused myocardial ischaemia with resulting hypotension and arrhythmia. Despite the associated decrease in arterial pressure, the anaesthetist elected to treat the ST elevation with a coronary vasodilator rather than resorting to the more conventional approach of treating the complication with a vasopressor. This therapy was highly efficacious.

One can only speculate as to the origin of the spasm. It has been shown that spinal or extradural blockade denervates the sympathetic nervous system two to three segments above the level of somatic block. Above the level of sympathetic blockade, compensatory vasoconstriction is seen, presumably in an effort to offset the reduction in peripheral resistance caused by the block. This reflex sympathetic activity would involve the cardiac sympathetic nerves causing coronary vasoconstriction and consequent ischaemia.

Prinzmetal suggested that the pathophysiology of the condition is increased tonus (spasm) of a large coronary vessel which is already partially occluded by atherosclerosis. This has subsequently been demonstrated by coronary angiography performed during the attack (MacAlpin and Kattus, 1967; MacAlpin, 1970; Silverman and Flamm, 1971; Dhurandhar et al., 1972; Oliva, Potts and Pluss, 1973; Gensini, 1975).

Levin, Wolk and Summers (1974) found that 27% of the patients had normal coronary angiograms. It is now recognized that patients with Prinzmetal's angina may have totally normal coronary angiograms.

The factors initiating coronary artery spasm have not been fully elucidated. The coronary arteries are supplied with both alpha and beta receptors, the former mediating vasoconstriction and the latter vasodilatation (Zuberbuhler and Bohr, 1965; Bohr, 1967; Macraven et al., 1971). It is known that alpha receptors predominate in the larger coronary vessels and the injection of adrenaline or noradrenaline in the patient who is beta blocked will induce profound vasoconstriction.

Yasue and others (1976) studied four patients with Prinzmetal's angina. These patients were given propranolol 40 mg and 3 h later adrenaline 0.4–0.5 subcutaneously. With the beta receptors blocked, the unopposed alpha activity of adrenaline was well demonstrated. Within a short time all patients experienced angina. This was associated with an increased arterial pressure and a reduction in heart rate. On a subsequent occasion the regimen was repeated and coronary angiography was performed during the attack. Severe spasm accompanied by ST segment elevation was demonstrated in all four patients. Both the spasm and the pain were rapidly relieved by nitroglycerin.

Is coronary vasoconstriction solely a result of sympathetic stimulation, or does it follow some parasympathetic–sympathetic interplay? Levy (1971) postulated that increased vagal activity results in stimulation of the preganglionic sympathetic fibres with release of noradrenaline at the post-ganglionic nerve ending.

In an earlier paper Yasue, Touyama and Shimamoto (1974) postulated that the parasympathetic nervous system played a pivotal role in initiating the attacks. They studied 10 patients with Prinzmetal's angina. Three of the patients had anginal symptoms at the time of the investigation, while the remaining seven had been symptom-free for more than 3 months. All 10 patients were given 10 mg of metacholine subcutaneously. In the three with symptoms, an attack of Prinzmetal's angina was precipitated, associated with ST segment elevation, while the symptom-free patients were not affected. When the three patients were given atropine, the subsequent injection of metacholine did not induce an attack. One of the patients was given phenoxybenzamine on the night before receiving a metacholine test and this prevented the attack. Administration of propranolol aggravated the symptoms.

Further evidence supporting the importance of the parasympathetic nervous system comes from studies on patients during rapid eye movement (REM) sleep (Nowlin et al., 1965; Murao et al., 1972). Variant angina is known to be associated with REM sleep. Acetylcholine is known to trigger REM sleep, while atropine has been shown to prevent it.

Management

Nitroglycerin is the mainstay of treatment. Its effect, when given either sublingually or i.v., is almost instantaneous. Endo and others (1975) described 35 consecutive patients whose symptoms, e.c.g. changes and arrhythmia were relieved by nitroglycerin. The value of atropine seems to be preventive rather than therapeutic and it should be used as part of the premedication in a patient with known Prinzmetal's angina.

Propranolol is contraindicated in the management of variant angina. By blocking the beta receptors, unopposed alpha activity of endogenous catecholamines can either precipitate or intensify coronary artery spasm. Calcium antagonists such as verapamil and nifedipine prevent calcium flux, thus relaxing the coronary vessels and preventing their responses to vasoconstrictive influences.

In a study of 12 patients with variant angina given nifedipine in appropriate doses, Goldberg and others (1979) reported that pain disappeared in 11 of the patients. None exhibited hypotension or tachycardia. Nifedipine withdrawal is associated with an aggravation of anginal symptoms and should not be discontinued before operation.

Patients in whom ventricular arrhythmia develops during an attack often fail to respond to conventional anti-arrhythmic drugs such as lignocaine or procainamide; calcium blockers are often effective (Heupler and Proudfit, 1979).

Since the pathophysiology is primarily one of spasm, it is not surprising that excision of the stenotic lesion is ineffective (Endo et al., 1975), whereas a bypass graft of the spastic section has been effective in two patients in this institution.

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ANGINE (VARIANTE DE PRINZMETAL) PENDANT UNE ANESTHESIE EXTRADURALE

RESUME

Un homme de 55 ans, subissant une intervention chirurgicale pour des varices après un blocage extradural, s'est plaint de douleurs dans la poitrine. Les variations de l'e.c.g. et l'examen ultérieur du coeur, y compris une angiographie coronaire, ont laissé penser à une angine de la variante de Prinzmetal. Les implications thérapeutiques de cet état sur des malades subissant une anesthésie et une intervention chirurgicale sont débattues dans cet article.

PRINZMETAL-ANGINA WÄHREND EXTRADURALER ANÄSTHESIE

ZUSAMMENFASSUNG

Ein 55 jähriger Patient entwickelte Schmerzen in der Brust während einer Operation für Krampfadern bei extraduraler Blockierung. EKG-Veränderungen und anschliessende Herzuntersuchungen einschliesslich Koronarangiographie liessen Prinzmetal-Angina vermuten. Die therapeutischen Bedeutungen dieses Zustandes bei Patienten unter Narkose für Operationen werden diskutiert.

LA VARIANTE PRINZMETAL DE ANGINA, DURANTE ANESTESIA EXTRADURAL

SUMARIO

El examen de un paciente masculino de 55 años de edad en proceso quirúrgico al respecto de varices y con un bloqueo extradural se quejó de dolor en el pecho. Los cambios en el electrocardiograma (e.c.g.) y el subsiguiente examen del corazón, incluyendo la angiografía coronaria, sugirieron el diagnosis de Prinzmetal, que es una variante de angina. Se discuten, seguidamente, las repercuisones terapéuticas de esta condición en pacientes sometidos a anestesia y a proceso quirúrgico.

Br. J. Anaesth. (1980), 52, 951P

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

BRISTOL MEETING
JULY 12, 1980

CHANGES IN THE CEREBRAL FUNCTION MONITOR COMPARED WITH CHANGING PLASMA CONCENTRATIONS FOLLOWING ADMINISTRATION OF I.V. ANAESTHETICS BY REPEATED BOLUS DOSES

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The cerebral function monitor (CFM) has been used in the management of i.v. anaesthesia and a relationship demonstrated between clinical levels of anaesthesia and the CFM trace (Dubois et al., 1978). A correlation between plasma concentration of alphaxalone when administered as a continuous infusion and the changes in CFM has also been shown (Savege, Zych and Dubois, 1978).

In this study, changes in the CFM have been compared with changes in plasma concentrations of anaesthetic agents in patients receiving regularly timed bolus doses of either thiopentone or Althesin. In addition, the changes in CFM were studied in several patients receiving repeated bolus doses of ketamine, methohexitone, propanidid or etomidate.

Healthy patients undergoing elective gynaecological or general surgery were studied. Biparietal electrodes were placed on the scalp, and a waking CFM trace recorded. An induction dose of i.v. anaesthetic agent was given over 20 s through a peripheral indwelling needle. Anaesthesia was maintained with incremental i.v. bolus injections of half the dose of the induction agent given over 10 s every 4 min. Blood samples for measurement of plasma concentrations of thiopentone or alphaxalone were taken through an indwelling i.v. cannula 15 s before and 60 s after each increment. The other anaesthetic agents were administered in a similar manner. The various patterns of change in the CFM were recorded. The patients breathed oxygen through a face-mask and Guedel airway, and heart rate and arterial pressure were monitored.

Plasma thiopentone concentrations were estimated by gas chromatography using a nitrogen phosphorus detector, and plasma alphaxalone concentrations by gas chromatography using an acylating agent and an electron capture detector.

The resulting pre- and post-incremental plasma concentrations of thiopentone and alphaxalone were plotted against the upper and lower levels of the CFM trace, and a good correlation was found. The lower level of the trace was found to be a better indicator of increasing plasma concentrations of i.v. anaesthetic agent than was the upper level. Inter-patient and inter-agent variation were evident, but there was a consistent trend.

Induction of anaesthesia by any of the induction agents used was followed by a rise of the CFM trace to a peak, followed by a fall and slow broadening of the band. As recovery began the trace rose and narrowed, while the incremental injections cause a further fall and broadening of the trace. The regular stepwise pattern thus obtained showed a within-agent consistency, but each agent developed a characteristic pattern which may reflect its cerebral pharmacokinetic properties when given as increments. In view of the known difficulties associated with sampling blood and estimating plasma concentrations, and the delays in movement of drug across tissues, measurement of CFM is likely to prove a more reliable method of assessing the anaesthetic action of i.v. agents on the brain.

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MIDAZOLAM—AN ALTERNATIVE TO THIOPENTONE?

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The need for an alternative induction agent to thiopentone still exists. Diazepam has been shown to have limited use as an induction agent as a result of its slow onset and long duration of action, and low water solubility. Recent reports have commented favourably on the new water-soluble benzodiazepine, midazolam. Indeed, Sarnquist and colleagues (1980) claim that it is a suitable alternative to thiopentone for induction of anaesthesia

In a preliminary study in volunteers using 5- and 10-mg (sub-anaesthetic) doses of midazolam maleate, we found that the drug showed slow onset of action (2–5 min for maximum effect) and a wide variation in response Its plasma half-life, however, was much shorter than that of diazepam (Dundee et al., 1980)

The effects of doses varying from 0.15 to 0.5 mg kg^{-1}, given over 30 s, were studied in 230 healthy patients (groups of 10 or 20) either unpremedicated or given an oral benzodiazepine (diazepam), a moderate (pethidine 50–75 mg with atropine 0.6 mg) or large (papaveretum 20 mg with hyoscine 0.4 mg) dose of opiate. Initially the maleate salt was used, but this was replaced by the hydrochloride when it became available. The "depth" of sedation was noted at 1-min intervals until the patient was asleep or for 5 min after administration, graded arbitrarily as nil, slight, moderate, marked or asleep with absent eyelash reflex.

The findings (table I) show a large individual variation in response to midazolam and a marked additive effect with opiate premedication. Diazepam was not as effective in this respect. In unpremedicated patients a dose of 0.5 mg kg^{-1} was found to be inadequate for some, while 0.15 mg kg^{-1} induced sleep in others.

TABLE I. *Percentage frequency of patients considered to be asleep by 5 min after i.v. midazolam*

	Dose of midazolam (mg kg^{-1})			
Premedication	0.15	0.2	0.3	0.5
Nil	20	15	50	60
Diazepam	—	35	50	75
Light opiate	—	50	85	100
Heavy opiate	—	85	100	—

Even with moderate drowsiness, patients tolerated a face-mask and volatile inhalation techniques. There was no recall, although the patients may have opened their eyes when the mask was applied. In contrast, patients assessed as "asleep" often responded to tracheal intubation or surgical stimuli. Our experience does not support the view that it is an acceptable substitute for thiopentone unless preceded by heavy premedication. However, its lack of tissue toxicity suggests that it should be investigated further as a light sedative in place of diazepam.

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AN INVERTEBRATE MODEL FOR THE STUDY OF GENERAL ANAESTHETIC AGENTS IN THE CENTRAL NERVOUS SYSTEM

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General anaesthetics have been shown to depress reversibly the depolarizing sodium-dependent responses to transmitters in invertebrate neurones (Barker, 1975; Judge, Norman and Walker, 1979). Barker (1975) found that pentobarbitone antagonized the acetylcholine (ACh) response in an identified neurone of *Otala* in a primarily non-competitive manner. In this study the effects of ketamine on postsynaptic responses of *Helix* neurones were examined and compared with the actions of thiopentone.

Intracellular recordings were made from identified neurones in the isolated brain of the snail, *Helix aspersa* (Judge, Norman and Walker, 1979). The membrane potential of the neurone was monitored and could be varied by injection of current through the recording electrode by means of a bridge circuit. Responses to either iontophoretically applied ACh or 5-hydroxytryptamine (5-HT) were obtained while the preparation was perfused with either normal Ringer solution or a solution of anaesthetic made up in Ringer.

Ketamine 0.05–0.35 mmol litre^{-1} and thiopentone 0.1–0.2 mmol litre^{-1} both reversibly depressed the sodium-dependent depolarizing responses to ACh of cell F1 in a dose-dependent manner. Ketamine was also found to depress the sodium-dependent depolarizing response to 5-HT in this cell. Reversal potentials of these responses remained unchanged in the presence of thiopentone, but were shifted by ketamine. Whereas thiopentone appeared to act non-competitively, the antagonistic effects of ketamine indicated a competitive type of interaction. These results indicate that thiopentone at these concentrations acts indirectly at the site of the receptor-coupled sodium ionophore. Ketamine appears to be producing direct effects on the postsynaptic neurone in addition to effects on the responses to applied transmitters.

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VASOACTIVE INTESTINAL PEPTIDE IN THE PERIOPERATIVE PERIOD

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Vasoactive intestinal peptide (VIP) is a polypeptide with 28 amino acids. It is present in the gut and the central nervous system (Pearce, 1976). It shows many homologies with the classical hormones secretin and glucagon. It has been implicated clinically in the Verner Morrison syndrome. It is a potent peripheral and splanchnic vasodilator, stimulates breathing and causes hyperglycaemia (Said and Mutt, 1970). Patients with tumours secreting VIP may become severely hypotensive during surgery.

In view of the potent vasodilator properties of VIP, this study was undertaken to determine if significant amounts are released during surgery under general anaesthesia.

In eight patients undergoing cholecystectomy, venous blood samples were taken before and after premedication, after induction of anaesthesia, following incision of the skin and peritoneum, during manipulation of the bowel, resection of the gall bladder, closure of the abdomen, after antagonism of relaxant and during the recovery period. In seven patients undergoing cardiac surgery with cardiopulmonary bypass, blood samples were taken before and after induction of anaesthesia, before and after heparin administration (at 1, 3 and 5 min), during cardiopulmonary bypass (after 10 min and 30-min intervals) and before and after protamine (at 1, 3, 5, 15 and 30 min). Both groups of patients were premedicated with papaveretum and hyoscine, anaesthesia was induced with thiopentone and maintained with nitrous oxide, oxygen and either fentanyl or papaveretum. Artificial ventilation was used and muscle relaxation was maintained with pancuronium. The blood samples (10 ml) were taken into Lithium–heparinized tubes containing aprotinin 200 µlitre (4000 KIU), centrifuged immediately and the decanted plasma stored at −20°C until assay. Assay was carried out using a specific radioimmunoassay (Mitchell and Bloom, 1978).

The blood concentrations of VIP did not incease above the normal adult value, 21 pmol litre^{-1}, in both groups of patients. Neither manipulation of the bowel nor the administration of protamine caused significant changes. In all patients there was a trend for the concentrations to decrease immediately after induction of anaesthesia, but they remained within the accepted normal range. The conclusion of this study is that VIP is unlikely to be a significant factor causing hypotension in otherwise normal patients undergoing surgery or cardiopulmonary bypass.

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ANAESTHESIA, SURGERY AND MOTILIN CONCENTRATIONS: A PRELIMINARY REPORT

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Motilin, a peptide with 22 amino acid residues (Bloom, 1976), is a gut hormone produced by the enterochromaffin cells of the duodenum and jejunum. It stimulates the smooth muscle of the gut, and its fasting blood concentration is 100 pmol litre^{-1}. Its release is facilitated by acidification and inhibited by alkalinization of the duodenum. It has effects which may be of interest to anaesthetists for two reasons: (1) it increases lower oesophageal sphincter tone, and (2) motilin concentrations change during anaesthesia and surgery and this may contribute to postoperative ileus as a result of an effect on the colon. Pathological postoperative ileus is now considered to be a result of passive dilatation of the colon by air in the first 48 h after operation when colon activity is sluggish. The air is propelled down the intestinal tract by the small gut which retains a higher intrinisic activity than the colon. The resulting gaseous distension of the colon converts a physiological ileus to a pathological colonic ileus (Woods et al., 1978).

The purpose of the study was to investigate the effects of premedication, surgery and anaesthesia on motilin concentrations.

Patients studied were undergoing cholecystectomy, hemicolectomy or inguinal hernia repair. They were allocated to three groups: no premedication (six, hernia); atropine only (12, cholecystectomy and hernia); papaveretum and hyoscine (12, colectomy and cholecystectomy).

The anaesthetic technique comprised a thiopentone–nitrous oxide–oxygen–halothane–pancuronium sequence and artificial ventilation of the lungs. No opiate supplements were administered. Venous blood samples were taken: before and 1 h after premedication, and after thiopentone, pancuronium, skin and peritoneal incisions, manipulation of the bowel, antagonism of relaxant, and before postoperative analgesic drugs were administered. Subsequently, further samples were taken for 4 days, on each occasion before the administration of analgesic drugs or oral intake. The time of return of bowel function was noted. Motilin was assayed using a highly sensitive and specific radioimmune assay (Bloom, Mitznell and Bryant, 1976). Changes of 3 pmol litre^{-1} can be detected with 95% confidence.

While awaiting surgery, irrespective of premedication, patients showed a 30–40% reduction in motilin concentration which was statistically significant; thereafter during anaesthesia and surgery there was no further significant change in concentration. On the first day after operation the concentration had returned to the range before surgery and the 2nd and 3rd days there was an increase in concentration between 40 and 80% which was statistically significant.

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MYOCARDIAL FUNCTION AND CRITICAL CONSTRICTION OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY: EFFECTS OF ENFLURANE

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Halothane produces significant dose-related depression of global and regional myocardial function. Depression of function of a particular region can be exaggerated by constricting the arterial supply to that region (Francis et al., 1980). If the left anterior descending (LAD) coronary artery is constricted, such regional depression is not reflected in the overall performance of the heart, and therefore may not be recognizable by conventional clinical monitoring. This paper describes the effects of enflurane studied under similar conditions.

Eight dogs, premedicated with morphine 0.3 mg kg^{-1}, were subjected to stepped increases in enflurane concentration in oxygen. This was achieved in increments of 0.55%, starting at 1.1% and proceeding to 3.3% under controlled ventilation.

Studies were conducted before and after critical constriction of the LAD artery. Global cardiac performance was assessed (e.c.g., aortic, left ventricular and left atrial pressures, aortic and distal LAD coronary blood flows, LV dP/dt, stroke volume and aortic blood acceleration) concomitantly with assessment of regional myocardial wall function in terms of changes in segment length. The latter measurements were made using miniature ultra-sonic length transducers implanted in subendocardial muscle; one pair in territory supplied by the LAD

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artery and another pair in territory supplied by the left circumflex (LC) coronary artery.

Constriction of the LAD artery was applied by means of a micrometer-controlled snare and was defined as "critical" when further constriction produced reversible deterioration in segmental function. Critical constriction was verified by demonstrating that the normal "hyperaemic" response to a 10-s occlusion of the vessel was suppressed.

Before constriction, dose-dependent decreases were observed in the following: mean arterial pressure by 32%, LV dP/dt by 49%, and cardiac output by 37%, culminating at 3.3% enflurane. At the same time, regional function was impaired: segmental end-diastolic length increased by 7% in both segments and systolic shortening was reduced by 40% in the LAD territory and 30% in the LC territory.

In the presence of critical constriction of the LAD artery a more marked pattern of global depression was observed. At 3.3% enflurane there was significantly more depression of mean arterial pressure by 44%, LV dP/dt by 57%, and cardiac output by 52%. Depression of regional function was evident. In the territory supplied by the constricted LAD end-diastolic length increased by 9% (significantly greater than pre-constriction), and systolic shortening was reduced by 52%. In the LC region, end-diastolic length increased by 7% and systolic shortening decreased by 25%.

It was concluded that, before critical constriction of the LAD artery, enflurane produced a marked reduction in segmental wall function and a matching depression of global cardiac function. Critical constriction produced slightly greater depression of LAD segmental function when compared with the LC segment, and significantly more depression of global function.

ACKNOWLEDGEMENTS

G. R. Cutfield is in receipt of an Overseas Research Fellowship from the Medical Research Council of New Zealand.

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CARDIOVASCULAR EFFECTS OF MIDAZOLAM (RO 21-3981) IN THE DOG

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Midazolam, a new i v induction agent has been introduced recently for clinical trials (Fragen, Gahl and Caldwell, 1978) The present study was undertaken to examine the changes which this drug may cause in the cardiovascular system.

Dogs were anaesthetized with methohexitone followed by chloralose. Following neuromuscular block induced with suxamethonium, the trachea was intubated and the lungs ventilated with oxygen-enriched air (Pa_{O_2} in excess of 23 kPa, Pa_{CO_2} and pH in the ranges 4.4–5.9 kPa and 7 24–7.33 units respectively). Femoral arterial and venous cannulae were inserted. In eight preparations cannulae were inserted via the right side of the heart to allow the determination of cardiac output by dye dilution. In other preparations the phrenic nerve was exposed in the neck and the renal sympathetic nerves retroperitoneally. The nerves were desheathed, immersed in mineral oil and efferent activity was recorded using silver/silver chloride electrodes.

In five dogs in which efferent sympathetic nerve activity was blocked with bretylium tosylate the effect of midazolam 1 mg kg^{-1} on vagally-mediated increases in heart rate evoked by electrical stimulation of the radial nerve was observed for 90 min (Norman and Whitwam, 1973).

Following the administration of midazolam 1 mg kg^{-1} there was a decrease in mean arterial pressure. The maximal effect was seen at 10 min when the mean pressure had decreased from 164 mm Hg to 116 mm Hg, after which recovery occurred, but this was not complete at 1 h (mean pressure 136 mm Hg). There was an associated increase in mean heart rate from 129 beat min^{-1}to 145 beat min^{-1} at 5 min, after which the heart rate decreased progressively to a mean value of 91 beat min^{-1} at 1 h. Cardiac output decreased from a mean value of 2.65 litre min^{-1} to 1.75 litre min^{-1} at 45 min and was still below control values (2.25 litre min^{-1}) at 60 min. This is in agreement with the work of Jones, Stehling and Zauder, (1978) and in contrast with the effect of diazepam and its solvent propylene glycol, which produce initially a decrease in both heart rate and arterial pressure. Midazolam caused an immediate reduction in activity in both phrenic and sympathetic nerves after which recovery started, but there was evidence of a persisting effect on the nervous system for more than 1 h.

Midazolam 1 mg kg^{-1} did not cause any reduction in vagally-mediated reflexly evoked changes in heart rate.

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APPARENT DIFFERENCES BETWEEN PULMONARY VOLUMES OF DISTRIBUTION OF OXYGEN AND NITROGEN MEASURED BY RE-BREATHING: A MEASURE OF FAULTY EXTRAPOLATION

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Suwa and Bendixen (1971) described the use of oxygen as an indicator gas for measuring lung volume by the re-breathing manoeuvre. This method has been re-examined using mass spectrometry (Centronic MGA 200) to measure lung volume by re-breathing with oxygen and nitrogen simultaneously.

The apparent volumes of distribution of the two indicators were calculated after straight-line extrapolation from their respective concentration traces to estimate the hypothetical concentration, $(Fm)_0$, for each gas, which would have resulted from complete mixing of lung and re-breathing bag gas in the first instant of the re-breathing manoeuvre. Suwa and Bendixen stated that, theoretically, addition of carbon dioxide to a concentration of 6% to the gas mixture in the re-breathing bag should improve the accuracy of this technique, but that in practice it did not change the results.

In six subjects, the apparent volumes of distribution of oxygen and nitrogen calculated from the straight-line extrapolation differed reproducibly from each other in a manner which varied with the size and direction of the change in gas concentrations between the control and re-breathing period. The differences were virtually abolished by the presence of 6–6.25% carbon dioxide in the re-breathing gas mixture, although the exact carbon dioxide concentration was critical.

When differences occurred, they were accompanied by discrepancies between the apparent $(Fm)_0$ for carbon dioxide, calculated as

$$1-(Fm)_0\,\mathrm{O_2}-(Fm)_0\,\mathrm{N_2}$$

and the expected $(Fm)_0\,\mathrm{CO_2}$, expected by the dilution of the control end-tidal carbon dioxide on mixing with the re-breathing gas. This suggested that the straight line extrapolation underestimated $(Fm)_0\,\mathrm{O_2}$ and $(Fm)_0\,\mathrm{N_2}$, and that the true line of extrapolation should have curved upwards from the straight line during the first few breaths of the re-breathing manoeuvre. Such an effect would be expected from a relatively large initial pulmonary output of carbon dioxide which declines substantially over the first few breaths.

With or without carbon dioxide in the re-breathing gas mixture, any discrepancy between the apparent and expected $(Fm)_0\,\mathrm{CO_2}$ can be used to adjust $(Fm)_0\,\mathrm{O_2}$ and $(Fm)_0\,\mathrm{N_2}$ to truer values in such a way as to give a unique estimate of lung volume and an improved estimate of the true line of extrapolation for each re-breathing manoeuvre. The ability to measure all gas concentrations in the system allows valuable checks on the internal consistency of the results.

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Mr I. L. Scott is in receipt of a Medical Research Council Studentship.

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RESPIRATORY GAS EXCHANGE IN VENTILATED PATIENTS

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A new method is described which measures respiratory gas exchange continuously in patients undergoing artificial ventilation. The method depends on mixing some of the inspired gas with the expired air via a shunt placed between the inspired and expired limbs of the circuit proximal to the ventilator. A constant flow pump (Edwards) sucks all the expired air, plus some of the inspired gas, through a dry gas meter which measures the total flow through the system. Recirculation of the expired air to the inspired limb of the circuit is prevented by ensuring that the inspired pressure is greater than the expired; a variable resistance placed on the shunt achieves this objective. The total volume of gas through the system is held constant by the pump and the difference in oxygen and carbon dioxide concentration between the inspired and expired/inspired mixture is measured using a paramagnetic oxygen analyser (Servomex) and an infra-red carbon dioxide analyser (Godart). The outputs from these analysers are amplified and, with the output from the dry gas meter, are displayed on digital voltmeters. The Servomex output has been modified to enable high inspired oxygen concentrations to be offset to zero. By amplifying the output from the Servomex and the capnograph, oxygen and carbon dioxide are displayed to 0.01% (of oxygen and carbon dioxide) accuracy. $V\mathrm{O_2}$ and $V\mathrm{CO_2}$ are calculated according to the Weir's formula (Weir, 1949).

It is possible to use the system with patients who are breathing high inspired oxygen concentrations and in the presence of anaesthetic gases. Uptake or excretion of nitrous oxide will introduce an error which will be minimal at steady state. Complete separation of inspired and expired gas is unnecessary. With certain ventilators, it is possible to use the system in intubated patients during spontaneous ventilation (with CPAP) or during IMV. Comparisons have been made with the Douglas Bag collection of expired air in dogs:

$$\dot{V}\mathrm{O}_{2\,\mathrm{STPD}}\,(\text{system})\,(\text{ml min}^{-1}) = 1.002\,\dot{V}\mathrm{O}_{2\,\mathrm{STPD}}\,(\text{Douglas Bag}) - 1.028$$

$$(n = 16;\ r = 0.999)$$

and in patients in the Intensive Therapy Unit:

$$\dot{V}\mathrm{O}_{2\,\mathrm{STPD}}\,(\text{system})\,(\text{ml min}^{-1}) = 1.032\,\dot{V}\mathrm{O}_{2\,\mathrm{STPD}}\,(\text{Douglas Bag}) - 4.6$$

$$(n = 12,\ r = 0.994)$$

The system is easily converted to the open-hood method of measuring $V\mathrm{O_2}$ in spontaneously ventilating subjects (Kappagoda, Stoker and Linden, 1974).

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USE OF LOW FRESH GAS FLOW OF ENTONOX WITH THE CIRCLE SYSTEM

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Despite its benefits of economy, decreased atmospheric pollution, conservation of warmth and humidification of gases, low-flow and closed-system anaesthesia is relatively unpopular at present. This probably results from uncertainty about inspired gas and vapour concentrations, especially when nitrous oxide is a component of the mixture.

In a mathematical model Holmes and Spears (1977) studied "very nearly closed-circuit" anaesthesia using Entonox (premixed 50% nitrous oxide in oxygen) as the fresh gas flow. They showed that 700 ml min^{-1} was close to the minimum safe fresh gas flow rate of Entonox for a whole body oxygen consumption of 225 ml min^{-1}.

We have tested this hypothesis in 55 patients, undergoing major gynaecological surgery, who were anaesthetized using either halothane in nitrous oxide with spontaneous ventilation and subarachnoid block analgesia (25 patients) or a technique using nitrous oxide supplemented with morphine and halothane and pancuronium to facilitate controlled ventilation (30 patients). The composition of gases within the tracheal tube was monitored continuously using the Centronic MGA 200 mass spectrometer as modified in this department (Davis and Spence, 1979).

Initially a fresh gas flow of Entonox of 6 litre min^{-1} was used for approximately 5 min until inspired nitrogen concentration has decreased to less than 5%. Fresh gas flow was then reduced to 500 ml min^{-1}, the inspired oxygen concentration decreasing slowly. To determine the fresh gas flow rate which produced a steady (within 1% over 30 min) inspired concentration of oxygen of 35%, additional nitrous oxide was added to the system to bring the inspired oxygen concentration rapidly to 35%. Thereafter, using a bracketing technique, the ideal flow rate for the desired inspired concentration was determined in each patient.

The mean flow rate in the patients who breathed spontaneously was 520 ml min^{-1}; with controlled ventilation it was 600 ml min^{-1} with a surprisingly wide range in both groups of 300–800 ml min^{-1}. There was no significant correlation between those flow rates and body weight or age in either group.

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HAND AND RESPIRATORY MUSCLE PARALYSIS PRODUCED BY ORG NC 45 IN MAN

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Org NC 45, a monoquaternary analogue of pancuronium, is a potent neuromuscular blocking drug that appears to be devoid of antimuscarinic activity at neuromuscular blocking doses (Durant et al., 1979). Preliminary clinical studies show it to be potent, relatively short acting and non-cumulative (Crul and Krieg, 1980). In this study we have looked at the onset of paralysis with regard to the adductor pollicis and the diaphragm and made some observations on the duration of recovery from paralysis with the drug.

Adult patients gave informed consent to the study. After induction of anaesthesia with thiopentone, the ulnar nerve was stimulated supramaximally at 0.1 Hz and the resultant twitch force of the adductor pollicis recorded. Respiratory muscle activity was recorded using a Wright electronic respirometer or an infra-red carbon dioxide analyser, or both. Doses of 25, 50, 75 or 100 µg kg^{-1} were studied.

The three largest doses always produced apnoea, but two patients failed to develop complete paralysis of the adductor pollicis. The onset of respiratory paralysis preceded that of the hand muscles. Apnoea occurred on average 1.2 min after the injection of these doses (range 0.8–1.8 min), whereas the maximum block (mean 99%, range 84–100) occurred 3.35 min after injection (range 1.6–6.8 min).

The average times from the first detectable effect in the hand to recovery to 25% of the initial twitch force were, for 50 µg kg^{-1}, 19.1 min (seven patients); 75 µg kg^{-1}, 30.0 min (nine patients) and for 100 µg kg^{-1} 26.8 min (nine patients). Once recovery started the rate of recovery of the twitch force averaged 5.9% min^{-1} and did not appear to be a function of the dose of drug used. When repeated injections were given, the rates of recovery were not altered and it was not possible to demonstrate significant accumulation of the drug. Residual paralysis could be antagonized by neostigmine.

In contrast with pancuronium (Norman, Katz and Seed, 1970) Org NC 45, although a competitive type neuromuscular blocking drug, produces a rapid onset of respiratory paralysis, has a shorter duration of action and appears to show little cumulative action.

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FURTHER STUDIES WITH ATRACURIUM

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It has been demonstrated that atracurium is a potent, highly selective competitive neuromuscular blocking agent with a relatively short action in anaesthetized man (Hughes, Hunt and Payne, 1980; Hunt, Hughes and Payne, 1980). Further studies have been carried out to investigate its clinical potential as a skeletal muscle relaxant, interaction with halothane and metabolism.

Endotracheal intubation was performed in six patients within 2 min of receiving atracurium 0.3 mg kg^{-1} i.v. and muscular relaxation was adequate during abdominal surgery for up to 20 min. Incremental doses of 0.1–0.2 mg kg^{-1} extended relaxation for a further 15–45 min. In three other patients, given doses of 0.54–0.62 mg kg^{-1}, tracheal intubation was accomplished within 1 min and these doses provided satisfactory relaxation for 30–45 min.

Interaction with 1% halothane was studied in nine patients using techniques already described (Hughes, Ingram and Payne, 1976). Recovery of the peak contraction was prolonged significantly and the rate constant for recovery reduced after doses of atracurium 0.2–0.6 mg kg^{-1} sufficient to block completely the tetanic response (table I). Similarly, the effect on the

TABLE I. *Tetanic response of the adductor pollicis muscle after neuromuscular paralysis by atracurium in the presence of 1% halothane (mean ± SEM). Significant difference from controls without halothane:* $^{*}P < 0.05$, $^{**}P < 0.01$

Dose (mg kg^{-1})	Onset of maximum effect (min)	Duration of maximum effect (min)	95% recovery of peak contraction (min)	Rate constant for recovery of sustained tetanus (% per min)
0.2 ($n = 3$)	2.0	12.3 ± 2.6**	39.2 ± 3.4*	9.0 ± 0.4
0.3 ($n = 3$)	2.0	12.7 ± 1.4	44.0 ± 2.9*	7.4 ± 1.5
0.6 ($n = 3$)	1.1 ± 0.2	31.7 ± 1.1	51.0 ± 1.9*	6.9 ± 1.0*

single twitch response was also enhanced. In the control group 74 ± 4.4% block was achieved ($n = 9$) after atracurium 0.2 mg kg^{-1}, whereas with halothane the block reached 91 ± 4.2% ($P = 0.05$).

Atracurium undergoes a non-enzymatic decomposition which can be enhanced *in vitro* by increasing the pH. In an attempt to demonstrate this mechanism *in vivo* we found that hyperventilation somewhat shortened recovery of the tetanic response in three of five patients given atracurium 0.2 mg kg^{-1}. Atracurium may also undergo an enzymic hydrolysis. Its half-life *in vitro* was 26.0 ± 0.55 min in human plasma ($n = 5$). Since we obtained a similar value of 24.5 min in atypical human plasma with deficient pseudocholinesterase, this suggests that, unlike suxamethonium, atracurium is not destroyed by this enzyme.

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A METHOD OF STUDYING THE DOSAGE OF THIOPENTONE

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There is great individual variation in the dose of thiopentone required to induce sleep. A study in 500 patients conducted at Aarhus (Christensen and Andreasen, 1978) demonstrated a significant decrease in thiopentone requirements with age, heavy premedication and cardiac disease. A more comprehensive study in 2200 patients has been conducted in Belfast in an attempt to identify a range of factors which influence the sleep-dose requirements of thiopentone.

For the purpose of this study the end point "sleep" was taken as the moment when the eyelash reflex was abolished. Thiopentone 2.5% was injected into a large antecubital vein; 2.0 mg kg^{-1} (to the nearest 25 mg) was given over 10 s and after a further 30 s the eyelash reflex was tested. If present a 25-mg increment dose was given and the eyelash reflex was tested again. Further increments were given as necessary until the eyelash reflex was abolished. The total dose was recorded.

A computer-compatible chart was designed to record the required patient and anaesthetic data and to enable statistical analysis of the results.

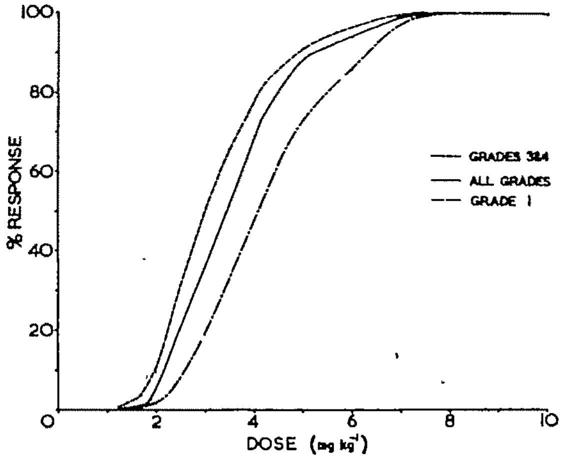

FIG. 1. Plot of sleep dose of thiopentone against response.

Figure 1 plots the sleep-dose of thiopentone against the cumulative frequency response in three groups of subjects.

(1) ASA I (unpremedicated)
Average sleep dose of thiopentone—4.20 mg kg^{-1} (SEM ± 0.06)
(2) ASA 3 and 4 (premedicated and unpremedicated).
Average sleep dose of thiopentone—3.29 mg kg^{-1} (SEM ± 0.09)
(3) All subjects (premedicated and unpremedicated).
Average sleep dose of thiopentone—3.65 mg kg^{-1} (SEM ± 0.03)

The dose–response curves show a log normal distribution which is a usual response pattern in drug dosage studies. This indicates that the method of study was sufficiently sensitive to identify factors likely to affect the sleep-dose of thiopentone.

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CORRESPONDENCE

PAIN RELIEF IN DENTAL SURGERY

Sir,—In regard to the letter to your Journal by Mr David McDonald (1979) concerning the training of non-anaesthetists to use drugs for pain relief in dental surgery, I wish to correct a misinformed statement in that letter.

The Faculty of Anaesthetists, Royal Australasian College of Surgeons has not endorsed any such training programme. From time to time the Faculty has advised upon resuscitation procedures and required equipment and drugs, in dental surgeries, and upon the undesirability of the single handed operator–anaesthetist.

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ANALGESIC PLASMA CONCENTRATIONS

Sir,—The increasing interest in the use of extradural opiates discussed in your recent editorial (Spence, 1980) has provided a timely illustration of the lack of meaning in the concept of "analgesic plasma concentrations".

Wolfe and Davies (1980) described the use of fentanyl injected extradurally as providing extremely satisfactory analgesia after surgery, without any adverse cardiorespiratory effects. They concluded from serial measurements of plasma concentrations in eight patients that the concentration of fentanyl in the plasma was unlikely to explain the observed results. As most of the values were less than the level of sensitivity of the assay (0.15 µg litre^{-1}), it is clear that the clinical results were indeed obtained with virtually insignificant plasma fentanyl concentrations. These workers then went on to suggest that a solitary value of 4.1 µg litre^{-1} in one patient is "probably less than that associated with an analgesic plasma concentration". This comment is open to misinterpretation.

The relatively short action of fentanyl has made the drug a favoured topic for research as well as clinical use. Tissue concentrations can be measured with a high degree of precision and the short action allows the study of the full time-course of the drug. Moreover, the relative lack of toxicity of fentanyl allows variations over a wide dose range. Unfortunately, the ability to measure a plasma concentration to a high degree of precision does not enhance the clinical relevance of the value obtained. Values in isolation are meaningless as they rarely represent a steady state. The situation following an i.v. bolus is very different from that after a prolonged infusion.

Hull and McLeod (1976) have shown that fentanyl 50 µg given i.v. results in plasma concentrations varying from 2.6 µg litre^{-1} at 2.4 min to 0.15 µg litre^{-1} at 2 h. Such a dose would at least initially provide analgesia in a conscious patient. This group has also emphasized the wide variation in plasma concentrations measured in different patients receiving low doses of the drug (Bower, Holland and Hull, 1976).

Following i.v. administration of moderate or large doses of fentanyl the duration of analgesic effect is not relatable to plasma concentrations (McQuay et al., 1979). Moreover, these workers could not detect clinical changes corresponding to "second peaks" in the plasma fentanyl decay curves measured within 45 min of the end of surgery. In two series of patients receiving either 25 µg kg^{-1} as a single dose, or 10 µg kg^{-1} followed by an infusion, the need for pain relief after operation occured at about the same moment (*ca.* 190 min from the start of operation). Interpolation of their data at this time yields a plasma fentanyl concentration in the "high dose" group of 6.9 µg litre^{-1} and in the infusion group a value of only 2.9 µg litre^{-1}. A third group in this study received significantly less drug, and complained of pain at 150 min but with a blood concentration of 5.8 µg litre^{-1}. As the patients at this stage were complaining of post-operative pain these blood concentrations cannot be regarded as analgesic in this context. More recent data (C. Prys-Roberts, personal communication) suggest that patients are generally comfortable after operation with fentanyl concentrations of 3–4 µg litre^{-1} and experience pain with blood concentrations near to 1 µg litre^{-1}.

It is clear that, even if we could standardize the measurement of analgesia, there is still a long way to go before such a parameter can be directly related to drug plasma concentrations. Rigg (1978) has already pointed out that plasma concentrations of morphine are not an objective indicator of pharmacological activity between patients. Even without the influences of other drugs and physiological variables, the time course of exposure to an agent must be considered before one can comment on the relevance of an individual plasma concentration. Presumably only at equilibrium would values have any significance so far as concentration at the receptor site is concerned.

The general model used for pharmacokinetic studies of fentanyl parallels the clinical use of the drug, with a bolus injection followed by a gradual decay according to three-compartment kinetics (Bower, Holland and Hull, 1976; Schleimer et al., 1978). Reaching a particular plasma concentration by this route presumably has a different clinical and pharmacological significance from achieving it following i.m. injection, extradural injection or a slow i.v. infusion. In these various situations discussion of plasma concentrations is meaningless unless they are placed in a dose/route/time context. Previous studies on fentanyl have sometimes combined data from different doses (Rigg and Goldsmith, 1976) and from different routes (Dunbar et al., 1967). It now seems we should be cautious not to introduce a third potential error from selective quotation of plasma concentrations of analgesics.

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DIAZEPAM AND THE NEUROMUSCULAR FUNCTION

Sir,—Drs Bradshaw and Maddison (1979) assessed neuromuscular function by measurement of adduction of the thumb caused by contraction of the pollicis adductor muscle. It would appear from the photograph and the diagram of the strain gauge that they are not in fact measuring adduction in its main line of force, but a compound movement—mainly flexion of the thumb, although distal stimulation of the ulnar nerve would not produce flexion directly. By having mainly the palmar aspect of the thumb directed against the strain gauge, adduction is not being measured. I feel that the line of force they have labelled in their diagram of the strain gauge is not adduction, but flexion.

The authors quote the work of Ali and Savarese (1976) as their reference for assembly of the correct measuring position. Ali and Savarese stated that many studies of neuromuscular function have not correctly defined the adduction component of their equipment. Have Drs Bradshaw and Maddison correctly measured adduction?

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Sir,—Perhaps the photograph to which Dr Carnie refers did not show clearly that the first metacarpal joint was fully through the ring of the transducer.

It is a common assumption that the adductor pollicis is the only small muscle of the thumb to be supplied by the ulnar nerve. Gray (1973) states that one head of flexor pollicis brevis is also supplied by the ulnar nerve and that a branch may be sent to the opponens pollicis. The ulnar nerve also supplies the palmar interossei. Thus, following stimulation of the ulnar nerve, it is difficult to isolate a movement of pure "adduction" of the thumb. In order to define the movement which may be produced by stimulation of the ulnar nerve, reference was made to the attachments of the small muscles of the thumb (Gray, 1973). The adductor pollicis oblique head has an origin and insertion similar to that of the flexor pollicis brevis, opponens pollicis and first interosseous muscles into the first metacarpal and the wrist. The transverse head of adductor pollicis has a totally different insertion into the third metacarpal. Thus, on ulnar nerve stimulation the exact direction of movement of the thumb will vary from individual to individual depending on which muscles are acting, their strength and the position of their attachments. A transducer which can respond accurately to a force acting in more than one plane must be used, and the one we described was designed to meet this requirement.

A further refinement has now been incorporated as lateral movement of the hand is prevented by the use of a single perspex bar.

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REFERENCE

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REGURGITATION DURING LAPAROSCOPY

Sir,—Dr Scott cannot have it both ways (Scott, 1980). On the one hand he says that during laparoscopy inhalation of gastric contents does not occur, yet he rightly points out the dangers to the lung of magnesium trisilicate, thereby implying that inhalation can occur.

The fasting surgical patient does not have an empty stomach (Hester and Heath, 1977). More specifically, fasting patients presenting for laparoscopy cannot be assumed to have empty stomachs (Tay and Chiu, 1978). In Tay's series, 70% of patients had a gastric pH of less than 2.5 unit and 32% had this low pH in conjunction with a volume exceeding 0.4 ml/kg body weight. I have shown that gastric contents can reach the pharynx easily and there is then only one more step before serious problems arise.

The majority of those studied by the Royal College of Obstetricians and Gynaecologists were probably inpatients, appropriately fasted and premedicated. The patients I anaesthetize are outpatients, usually without premedication and often in some turmoil following their journey and admission to hospital. There is always the possibility that outpatients will have ignored the instructions regarding fasting. What is more common however, is that they fast for excessively long periods which, in my experience, verified elsewhere (Hester and Heath, 1977), can lead to large volumes of very acidic gastric contents.

Patients presenting for laparoscopy are at risk. Magnesium trisilicate is not now the alkali of choice, but there are alternatives. I believe that metoclopramide, by increasing lower oesophageal sphincter tone, hastening gastric emptying and preventing vomiting, is an appropriate drug to use.

These young women are usually otherwise healthy, often undergoing an investigative procedure. It is imperative that the anaesthetic technique is designed to keep the mortality rate at zero and the morbidity rate to the absolute minimum.

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TYMPANIC MEMBRANE RUPTURE DURING NITROUS OXIDE ANAESTHESIA

Sir,—The use of nitrous oxide has been associated with the expansion of a pneumothorax (Eger and Saidman, 1965; Eger, 1974), an increase in intraocular pressure (Fuller and Lewis, 1975), and increased intracranial tension following pneumoencephalography (Artru, 1978). Impairment of hearing following pressure change in the middle ear has been reported in susceptible patients (Patterson and Bartlett, 1976), but tympanic membrane rupture is a rare complication. Owens, Gustave and Selasoff (1978) reported two patients who had pre-existing ear disease.

A 28-yr-old woman weighing 75 kg was admitted for late termination of pregnancy and laparoscopic sterilization. She was healthy, but had had a mild cough 2 weeks earlier for which an antibiotic had been prescribed. There was no past history of earache or hearing deficiency.

Labour was induced by extraamniotic prostaglandin E2 and an infusion of syntocinon 40 i.u. in 500 ml of 5% dextrose was instituted. Eight hours later a 20-week-old fetus was delivered. The following morning the patient received papaveretum 15 mg and hyoscine 0.3 mg; anaesthesia was induced with thiopentone sodium 350 mg; tracheal intubation was facilitated by alcuronium 20 mg. Anaesthesia was maintained with nitrous oxide 6 litre min^{-1}, oxygen 4 litre min^{-1} and halothane 0.5%, and intermittent positive pressure ventilation performed using a Penlon-Oxford ventilator delivering a tidal volume of 10 ml kg^{-1} body weight at a frequency of 12 b.p.m. The patient was placed in the lithotomy position and the retained products of conception were evacuated; ergometrine 0.5 mg was given i.v. to promote uterine contraction. Uterine bleeding continued, so a further dose of ergometrine 0.5 mg was given, and an i.v. infusion of Hartmann's solution was commenced. The patient was placed head-down and laparoscopic sterilization performed using a carbon dioxide pneumoperitoneum. During this procedure blood was noticed in the right external auditory meatus. This was removed, no further bleeding was noted, and surgery was completed uneventfully. Antagonism of neuromuscular blockade was achieved with neostigmine 2.5 mg and atropine 1.2 mg, and the patient made an uncomplicated recovery.

The following morning the ears were examined and a perforation of the right tympanic membrane was found. The only complaint made by the patient was of some "heaviness" on the affected side. She was referred to a Consultant Otolaryngologist who believed this to be an acute atraumatic rupture of the tympanic membrane, an opinion supported by the fact that it healed completely without treatment in 4 weeks.

I believe that nitrous oxide was the agent most likely to be responsible for this rupture.

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CARDIOVASCULAR RESPONSES TO THE SITTING POSITION

Sir,—In a recent issue, Dalrymple, MacGowan and MacLeon (1979) noted considerable haemodynamic changes when patients were raised from the supine to the sitting position during neurosurgical procedures. They described marked decreases in cardiac index, stroke volume, Pa_{O_2} and $\dot{Q}_s/\dot{Q}_t$ and a significant increase in $(PA_{O_2}-Pa_{O_2})$ and total peripheral resistance. They concluded that the maintenance of normotension in the sitting position did not necessarily signify an adequate circulatory status.

There is a considerable cardiovascular challenge involved in changing from supine to the sitting position in the relatively healthy patient. A "stable" arterial pressure may be recorded in the presence of an inadequate or marginal perfusion and care should be exercized in subjecting the elderly or poor-risk patient who does not have active compensatory mechanism in this position.

Albin and others (1974) studied the cardiovascular responses in eight patients aged 41–56 yr, all being ASA physical status I except for one patient who was ASA II. All patients underwent posterior fossa cranial nerve exploration and had no evidence of intracranial lesions nor increased i.c.p. Premedication, anaesthesia induction and maintenance and ventilation were standardized. Appropriate catheters were inserted and cardiac index (indocyanine green dye dilution cardiac output and body surface area measurements), oxygen transport (cardiac output and oxygen content) and systemic vascular resistance (SVR) calculated from cardiac output and arterial pressure measurements. These indices were studied under five conditions—supine, at 45°, at the 90° sitting position (immediately), at the 90° position 30 min later, and in the supine position after the procedure. No significant changes occurred until the patient was changed to the 90° sitting position when CI and oxygen transport decreased by about 20% from baseline supine control; SVR increased by 80% and mean arterial pressure increased by 40%. These values returned to control within 15 min of return to the supine position.

In a review of 400 patients who had neurosurgical procedures in the sitting position, we noted that two patients developed a myocardial infarction within 24 h of surgery and both were more than 65 years of age.

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OXYGEN TRANSPORT DURING DOPAMINE INFUSION

Sir,—Apparently Dr Chamberlain (1980) is challenging the initial statement in the concluding paragraph "... dopamine not only increased oxygen delivery . . . but it also increased overall oxygen utilization" on the grounds that the changes in oxygen availability and in some cases the changes in $\dot{V}O_2$ were not *statistically* significant. The statement was based on what we felt was a clear trend in the data, bearing in mind that the experimental model used was that of a fixed dosage regime.

The statement was used to place our own results within the context of what is known about the pharmacology of catecholamines in general and dopamine in particular.

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REFERENCE

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NEUROMUSCULAR PHARMACOLOGY

Sir,—It is most unfortunate that the interesting and informative article under the above heading by Drs Lee and Katz (1980) should contain an uncharacteristic, imprecise statement which ought not to go unchallenged. They state "the popular legendary notion that young infants are very sensitive to tubocurarine may represent anecdotes of pathologically sensitive responses of the few very sick infants who may be hypothermic, hypoxic, dehydrated, acidotic and hypocalcaemic". Lee and Katz noted that recent work suggested that reasonably healthy small infants may be more resistant rather than more sensitive to pancuronium, tubocurarine and suxamethonium. The importance of variation of response at different ages in this group of paediatric patients was not stressed, in particular in infants less than 1 month old and principally in those less than 10 days old.

Stead (1955) originally showed the increased sensitivity of the respiratory muscles of the newborn to tubocurarine and Bennett and others (1975) observed apnoea when reduced doses of pancuronium were given to newborn infants. Using the clinical criteria of full control of pulmonary ventilation and excellent relaxation, Bush and Stead (1962), in a large series of healthy newborn infants, suggested that the newborn during the first 28 days of extrauterine life showed a decreasing sensitivity to tubocurarine. Bennett and his colleagues (1976) confirmed this clinical finding. The study by Goudsouzian, Ryan and Savarese (1974) on the neuromuscular effect of pancuronium was performed in a series of 17 patients aged 5 weeks to 7 yr and hence the effect of this relaxant was not studied in newborn infants. Goudsouzian and his co-workers (1975), when re-evaluating the dosage and duration of action of tubocurarine in the paediatric age group, found that in the group in whom the age was less than 2 months, there was a greater variation in response than in the other age groups and this was most marked in those less than 10 days old. Similar wide variations were seen in a subsequent study using metocurine (Goudsouzian, Liu and Savarese, 1978). An article by Goudsouzian (1980) in the same issue as the review by Lee and Katz on the maturation of neuromuscular transmission in the infant, suggests that there are a number of parameters of neuromuscular transmission in the infant that are different in the newborn compared with older infants and children. Thus the contraction time was slower, the train-of-four ratio was less, post-tetanic facilitation and the tetanus : twitch ratios were less in infants less than 1 month old. These observations may be explained partly by changes occurring in the muscle itself, by changing from fast to slow types, and at the neuromuscular junction by a diminution in the safety factor for transmission as observed in the diaphragm of young rats (Kelly and Roberts, 1977). Goudsouzian (1980) in his careful investigation concludes that "one cannot come to a definite conclusion from this study".

The measured twitch responses of the thumb muscles under halothane anaesthesia are so fundamentally different from the clinical criteria used for full control of diaphragmatic movement using only nitrous oxide in oxygen that a valid comparison is impossible. Obviously important changes are taking place in neuromuscular transmission at this age and it is not unlikely that these changes vary in different muscle groups. Until this academic matter is resolved, it is to be hoped that in neonatal anaesthesia the dose of muscle relaxant will be administered to produce the desired clinical effect and not to assume that the thumb muscle responses represent a true picture of neuromuscular transmission in all muscles of the newborn. It is of interest that the dose found by Goudsouzian and colleagues (1975) to produce 95% reduction of muscle twitch in the newborn is remarkably similar to that used clinically. However, in older infants and children this dose is considerably less than that used clinically in our practice and does not, in our hands, produce diaphragmatic paralysis.

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Sir,—We appreciate the above comments regarding increased neuromuscular sensitivity in the newborn infant and heed the experience and the advice of the panel of distinguished experts in paediatric anaesthesia. In our article (Lee and Katz, 1980), we reviewed some of what we deemed better conducted recent studies in paediatric neuromuscular pharmacology and made the above-quoted statement accordingly. Whereas we discounted the significance of a here-to-fore overwhelmingly accepted doctrine and attempted to offer an explanation for it, we did not intend to deny it totally. Admittedly, it is our negligence to leave out the classic observations entirely. The statement by Dr Bush and his colleagues should have corrected this deficiency. However, we would like to answer the challenge made by them, and extend the discussion on some important concepts in clinical neuromuscular pharmacology.

There are fundamental differences between the diaphragm and the thumb, young rats and young infants, breathing and twitching, and particularly relaxation, apnoea and neuromuscular block. Young infants have larger abdomen and softer abdominal tone than adults and are more readily rendered apnoeic and maintained relaxed. However, although infants may be very "susceptible" to neuromuscular block, apnoea and relaxation do not prove that they are very "sensitive" to blockade in the diaphragm, the abdominal musculature, or the thumb. As a matter of fact, most articles referred to by Dr Bush documented the reversibility and safety of commonly used neuromuscular blockers, and successful restoration of respiratory muscle power suggests that the diaphragm might not have been paralysed as it had appeared.

The recent report by Goudsouzian (1980) on neuromuscular maturation, to which we had no access when we wrote our article, documented the neuromuscular abnormality of the newborn infant observable in the thumb under halothane anaesthesia. It did not document increased sensitivity to any relaxant in any muscle. As quoted above, Dr Goudsouzian *did not* come to a definite conclusion from that study. The transition from young to old neonates may be in the muscle but not in the transmission. Receptor occupation theory cannot be applied directly here. The 3–6% train-of-four fade in the thumb observed in young infants has not been confirmed by reduced neuromuscular reserve or abnormal receptor occupation in the diaphragm. In this respect, there exists an obvious conflict. As pointed out by Goudsouzian (1980), the thumb twitch seems to mature by a slow-to-fast muscle conversion, but the diaphragm matures by fast-to-slow conversion. If one uses the former mechanism to explain young infants' sensitivity in the thumb by virtue of slow muscle being more sensitive to tubocurarine, how can one explain their being also more sensitive in the diaphragm?

Careful examination of the data presented by Dr Goudsouzian and the comments made by Dr Bush suggest to us an explanation for the increased susceptibility of the young infants, if indeed they are more susceptible.

Respiratory movement is tetanic contraction, as is every physiological movement. Young newborn infants have weaker tetanus relative to the twitch (Goudsouzian, 1980), or reduced "tetanic spare". Therefore, at the same degree of block of the twitch, the respiratory muscle function (tetanic movement) might be more depressed. This, plus the possibly weaker respiratory drive, the pot-belly, and other factors increasing the susceptibility of the respiratory muscles to neuromuscular blockade in young infants might give the theoretical basis for the clinical observation of Dr Bush that newborn infants are sensitive. To avoid confusion, let us point out that very young infants have reduced tetanus : twitch ratio, that is, a reduced "tetanic spare", but not an increased tendency to tetanic fade (Goudsouzian, 1980). Previously, Kelly and Roberts (1977) observed that diaphragms of younger rats (30 days old), have reduced transmitter mobilization compared with those of older rats (110 days old). Mobilization failure would cause tetanic fade. Since young infants do not have increased tetanic fade, they might not share with young rats the propensity to mobilization failure. In other words, even if young infants were very susceptible to neuromuscular block, data obtained from young rats 30 days old should understandably give no precise clinical implications in neonatal anaesthesia and do not support the contention that infants may have mobilization failure. These rats are too old to be compared to neonates because rats wean before 21 days and reach puberty at 60–90 days.

In clinical practice, the real difference between newborn and older children may not be entirely that Dr Bush has to give less relaxant to the newborn. The real difference may be, at least partially, that he has to give more relaxant to older children, when doses of relaxants he gives for apnoea are compared with doses we would normally give for relaxation. If older children have stronger tetanus, are more resistant to respiratory depression, and Dr Bush and his colleagues use neuromuscular blockers to achieve apnoea, this indeed may be the case. It should be observed that, whether it be the thumb, the diaphragm, or the abdomen, a just 100% depression of the twitch may be equivalent to only 85% depression of the tetanus. Even if the diaphragm and the abdomen are assumed to have the same sensitivity as has the thumb, twitch for twitch and tetanus for tetanus, the residual 15% tetanus could be translated into a great deal of "bucking" or "tightness" which may be difficult to eliminate. As a result, older children under light anaesthesia may require a disproportionately large dose of relaxant to produce apnoea. That is why we are prejudiced to believe that it is more economical to use anaesthetics instead of the neuromuscular blockers for relaxation, once a reasonably profound block has been produced. This reasoning is in accordance with our philosophy of meticulous monitoring of the twitch.

In our article, we have carefully defined the purpose of monitoring. Specifically, monitoring should not replace clinical judgment, but should eliminate difficulty in the restoration of muscle power and aid differential quantitative diagnosis. In agreement with Dr Bush, we have always stressed individual variability in response, in adults as in infants, and therefore the importance of clinical observation and clinical judgment. We never advise others to give relaxants to newborn infants until the twitch is eliminated. Instead, we stress that in children or in adults, the anaesthetist should think twice before giving more relaxant if the twitch has been well depressed. Obviously, this touches upon an unrelated philosophical issue.

In all fairness, we agree that further study may prove newborn infants sensitive to non-depolarizing neuromuscular blockers. Also, while older children may have more sensitive thumbs than diaphragms, young infants may have more sensitive diaphragms than thumbs. Even if newborn infants require the same mg kg^{-1} dose of relaxant as older children do, they may still be considered sensitive if they require a smaller mg m^{-2} (b.s.a.) dose, or a smaller μg ml^{-1} serum concentration. Furthermore, young infants are more readily rendered apnoeic and maintained relaxed, and may as a result require less neuromuscular block for the same degree of relaxation. However, no properly controlled studies have convinced us that young infants are very sensitive in terms of ease of blockade of neuromuscular transmission. The effect of age is small when compared with the background normal individual variability in sensitivity.

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Goudsouzian, N. G. (1980). Maturation of neuromuscular transmission in the infant. *Br. J. Anaesth.*, **52**, 205.

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Lee, C., and Katz, R. L. (1980). Neuromuscular pharmacology. *Br J. Anaesth.*, **52**, 173.

VIRAL HEPATITIS

Sir,—We read Professor Strunin's editorial (1979) on viral hepatitis with interest and would agree with most of his comments. However, we think that his statements on the protection of individuals accidentally exposed to Hepatitis B virus (HBV) require clarification.

Exposure to infection arises from contact with the blood or body secretions of a patient in the acute, convalescent or carrier stages of HBV infection. The transmission of infected material may be by accidental stabbing with a contaminated needle or other sharp instrument; however, transmission may also be by prolonged and extensive skin contact, contamination of an open wound or sore, contact with the conjunctiva, or contact with mucous membrane (mouth, genital tract etc.).

We agree that it must be established that the "donor" material is infected: this is done by testing immediately for Hepatitis B Surface Antigen (HBsAg) by the most sensitive method available. The person at risk should be tested for HBsAg and antibody (anti-HBs) if the latter test is available and the results obtainable within a few hours. If the donor is HBsAg-positive, specific hyperimmune anti-HBs serum should be injected as soon as possible, preferably within 48 h of exposure; this may be followed by a second dose 1 month later. In practice it should be possible to test both donor and victim for HBsAg within 5–6 h; then a prompt decision to inject or withhold antiserum should be made. If exposure to infection occurred 24–48 h before the status of the donor was known or if laboratory results are not available for some time, then the decision to immunize should be made immediately, without waiting to learn the HBsAg status of the victim.

We were confused by the statement that "the subject should have standard liver function tests". Who is the subject—the donor or the recipient of the infected blood, and why is it necessary to test the liver function of either? We are convinced that it is important to give passive protection with hyperimmune anti-HBs serum as soon as possible to those who have been exposed to the risk of Hepatitis B by either inoculation or gross contamination with the blood or body secretions of a Hepatitis B patient or carrier; treatment must not be delayed to await the results of tests.

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Strunin, L. (1979) Viral hepatitis. *Br. J. Anaesth.*, **51**, 913.

BOOK REVIEWS

Mechanisms of Pain and Analgesic Compounds. (Miles International Symposium Series, No. 11.) Edited by R. F. Beers, jr and E. G. Bassett. Published (1980) by Raven Press. Pp. 496; illustrated; indexed. Price $51.35.

This book provides comprehensive coverage of recent studies concerning mechanisms of pain production and appreciation. It is divided into six sections and boasts about 1200 references and so is a review in every sense of the word.

Its value to a practical anaesthetic library will be limited though, as a great many of its pages describe contributions to a fairly specialized research field. However, there are some extremely interesting chapters particularly in Section A (for which J. J. Bonica acts as introducer and moderator) concerning the clinical contributions to the understanding of pain mechanisms, and in Section C (where the introducer and moderator is H. W. Kosterlitz) which provides some very interesting reading on the endogenous pain compounds. Other interesting contributions concern the design and interpretation of pain research techniques.

The titles to some of the chapters are rather long-winded and the language, for this side of the Atlantic, is rather verbose, but it is a book that any department involved in pain research would not want to be without. For the anaesthetic department without such an interest, however, it would be an extravagance.

K. Rogers

Anaesthesia for Children. Including Aspects of Intensive Care. By T. C. K. Brown and G. C. Fisk. Published (1979) by Blackwell Scientific Publications, Oxford. Pp. 400; illustrated; indexed. Price $29.00.

The appearance of this book, which has been eagerly awaited, represents the culmination of several years spent by Drs Brown and Fisk in its preparation. As the authors explain in the first pages, it owes its inception to the fact that the late Dr John Stocks, when Director of Intensive Care and Anaesthesia at the Royal Children's Hospital, Melbourne, produced a booklet entitled *Paediatric Anaesthetic Notes.* These were intended as a guide to practice within his own hospital, but because they contained so much useful and practical information, they were eagerly sought after by anaesthetists involved in this field, worldwide. It became clear to Dr Stocks that, using this as a basis, a book could be produced which would satisfy a demand. His untimely death in 1974 left this aim unfulfilled and we owe a considerable debt to Dr Kester Brown for his determination to complete the project.

The result is a book of 400 pages which is the only up-to-date paediatric anaesthesia textbook currently available. It is comprehensive in its content; the 33 chapters relate to almost every aspect of paediatric practice and its five appendices at the end give important additional information.

Many of the chapters are of a high order, both in content and presentation, for example "The child in hospital", "Anaesthetic management including intubation" and "Neurosurgical anaesthesia". Some chapters, however, seem to have been allocated excessive space, for example "Intravenous equipment and its use", and this space might have been used to expand others, for example details of the management of respiratory assistance. This could increase the value of the book to the anaesthetist who needs advice. A chapter devoted solely to the management of airway problems, of which the authors have considerable experience, would also be welcome.

The standard of photography and presentation is exceptionally high and much information can be obtained from the illustrations. Further information could be given in the text to relate to these, for example the Adams McLelland valve is often shown in use, but is not described in the section on anaesthetic apparatus.

This book transmits the dedication and enthusiasm of the Melbourne and Sydney anaesthetists. It is selective in choosing aspects of information and practice which are important to the anaesthetist when dealing with a child or infant patient and is to be recommended.

John Inkster

Automatic Ventilation of the Lungs (3rd edn). By W. W. Mushin, L. Rendell-Baker, P. W. Thompson and W. W. Mapleson. Published by Blackwell Scientific Publications, Oxford. Pp. 887; illustrated; indexed. Price £37.50.

It is more than 10 years since the second edition of this book was published. The apparent delay in the appearance of the much-rumoured third edition is completely vindicated by this volume, which must be the finest book of its type this reviewer has ever read.

The book has been increased in length by only 46 pages, and the pocket inserts in the cover of the second edition have been put in the text (which is an improvement, because inserts never stay with the volume). The book could have become enormous, but the authors have carefully chosen the instruments they describe as those readily available, so that instruments of interest to the "ventilator buff" are left out and the volume is a manual for ventilator usage as well as a valuable research reference volume. The reference lists are so comprehensive that there must be very few omissions.

The book can be divided into two parts: a section on the various aspects of controlled ventilation of the lungs—physiological, clinical, physical, control and historical (eight chapters) and a second section of 88 descriptions of various ventilators plus an appendix consisting of a glossary, a list of acronyms and a list of manufacturers.

The first section on the various aspects of controlled ventilation can be read consecutively without mental indigestion; in fact the reviewer found it difficult to put down. There may be some slight differences of opinion on the emphasis given to various matters in the physiological, clinical and physical aspects described, but in such a complex subject which was originally based upon empiricism and later on vast experience, such a response from the reader will occur. This section must be required reading for all who ventilate the lungs artificially in either the operating theatre or the intensive care unit. No candidate for the Fellowship Examination who has read and understood the basic principles and 50% of their implications need have doubts about their prowess in this subject. All of these sections have been reviewed and updated, but the section on the historical aspect has received meticulous attention. It is superb, it read like suspense fiction, but it was true and was profusely illustrated. The reviewer often had to put the book down when the revelation "so that is why it happened" occurred. An example is the development of fluidic logic control; it is firmly stated that Henri Coanda had nothing to do with the development of such control, but how well is this development detailed. The authors have traced and presented a photograph of Coanda's jet aircraft of 1910. This sort of scholarship is evident throughout the book.

The physical aspects have been further developed, as has the concept of the butterfly diagram used to show the relationship of the principal parameters involved in automatic ventilation of the lungs; there are now detailed six functional specifications. To learn to use this butterfly concept and diagram is not easy, but it does repay the effort. There is no need to learn the butterfly layout; once the principles are mastered, any ventilator presented by an eager sales representative could be analysed without reference to the manufacturer's optimistic claims.

The authors were so wise not only to keep these general sections, but to increase their scope, they could stand alone.

The second section detailing the characteristics of individual ventilators was a lengthy task for the reviewer. It cannot be read other than sporadically, but the high standard of the first section was maintained throughout the 88 different descriptions.

The authors have deliberately avoided using modern respiratory notation, in order not to confuse clinicians. There is an unfortunate jargon in this subject which has grown up amongst the users; I believe it must be rationalized I greatly regret that these authors have not attempted the task, for who could do it better? Their precision and economy of words are so evident; thus "respirator" is finally laid to rest with the words that "the authors note with regret . . : it should more properly be reserved for apparatus designed to filter contaminants from the inspired air".

If it takes 10 years before the fourth edition appears it is of little importance, because this text cannot become dated in that time. The book is essential for every medical library, anaesthetic department and intensive care unit. I need a personal copy and the reviewer is given a presentation copy; but I so enjoyed reading and reviewing the book I would have bought it. Now the department must buy its own!

John S. Robinson

Preparation for Anaesthesia. Edited by A J. Stevens. Published (1980) by Pitman Medical Ltd Pp. 453; illustrated, indexed. Price £22.50.

The Editor compiled this volume because he felt that preparation for anaesthesia was not well covered in the existing textbooks, and to emphasize the importance to the patient, both in psychological and medico-legal terms, of the close involvement of the anaesthetist in assessment before operation He has selected a wide variety of topics, some of which are not readily accessible except in the largest of the standard textbooks.

All multi-author books tend to suffer from overlap, repetition and uneven standards, and Dr Stevens has allowed his contributors a very free rein. Not only does he allow overlap between authors, but some have been permitted to encroach from the preoperative to the intraoperative period. This would not matter if space were unlimited, but it has resulted in one or two potentially valuable chapters, for example those on unusual medical conditions, being reduced to little more than checklists. Standards vary considerably; outstanding are those sections on local anaesthetics by Wildsmith and Scott, spinal and extradural blocks by Rubin, and pregnancy by Bryson, although all these subjects are already extensively covered in the literature. Stevens' own chapters on monitoring and the safety of equipment reflect his concern for the paramount importance of safe practice in its widest sense. Conversely, the chapter on resuscitation following trauma is disappointing, and appears to have been written for a readership less knowledgeable than anaesthetists. Authors have obviously been discouraged from making detailed reviews of the literature, a practice which makes for easy reading, whilst some key references are included.

Unfortunately the chapters are arranged in an arbitrary order, resulting in lack of continuity, whilst coverage of topics is not comprehensive. Respiratory disease is admirably and concisely dealt with, from basic physiology to clinical application, in 20 pages by Milledge. In contrast cardiac assessment, surely equally important, appears neither amongst the contents nor in the index; eventually it may be tracked down in Atkinson's chapter on inpatient anaesthesia. Renal and hepatic disease appear as a number of isolated comments scattered amongst several chapters. Haematology on the other hand, perhaps of less immediate concern to anaesthetists, receives three detailed chapters and a total of more than 60 pages. As a result of this, the anaesthetist who encounters problems on his preoperative ward round will not easily find the answers in this volume, and sometimes he will not find them here at all.

The binding is strong, the print is clear, but the layout of the pages is irritating—not only do the tables not stand out from the text, but they often appear on different pages from their reference in the text.

I agree with the editor when he stresses that assessment before operation is the responsibility of the anaesthetist directly concerned with that patient's care, and no one else. This volume brings home the extent of that responsibility, but it is a pity that it does not provide access to all the information needed in order to assume it. To this extent, therefore, its objective is not achieved. However, one of its more interesting aspects is that the editor has not turned to the most obvious authorities in each field, but has introduced a number of less well-known writers, many of whom have responded admirably to his challenge, and offered a refreshingly new slant on their topics.

Aileen K. Adams

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Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27.50, Airmail £50 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

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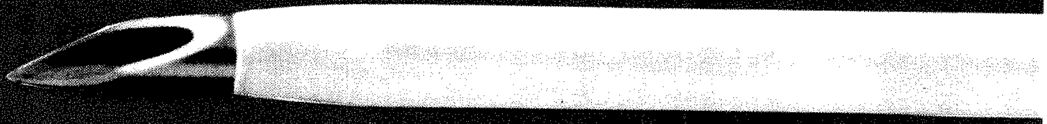

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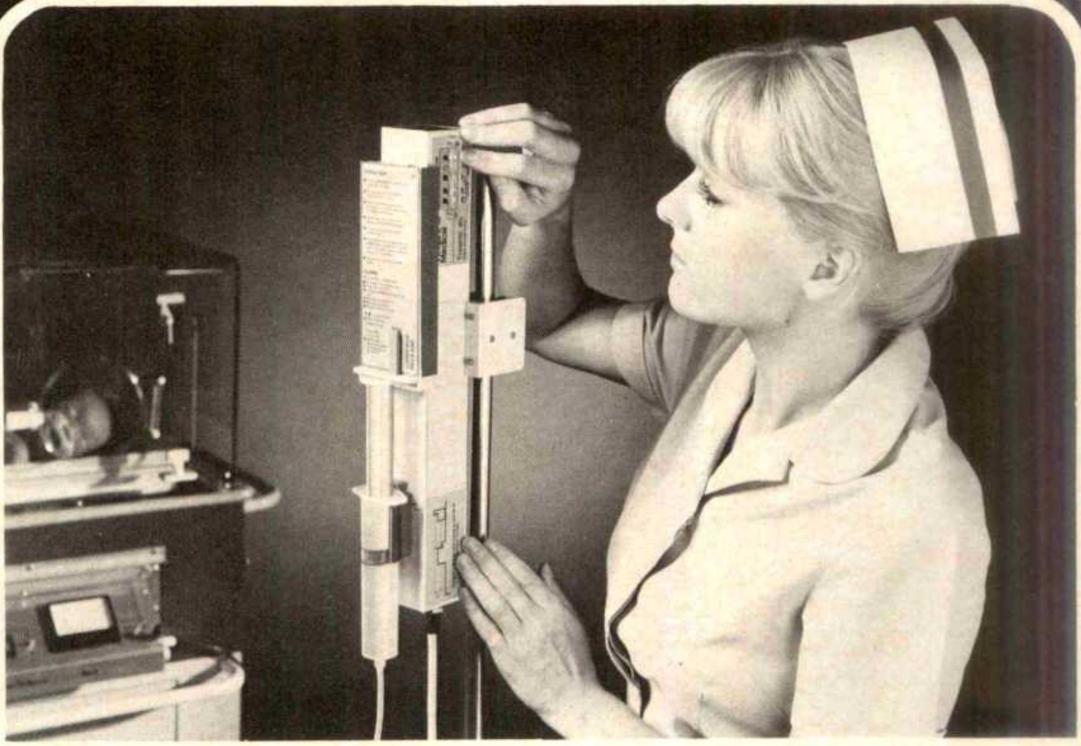

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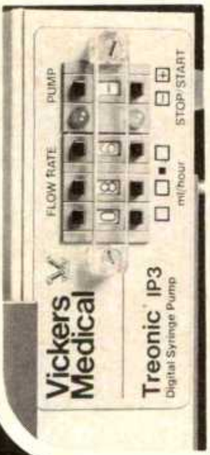

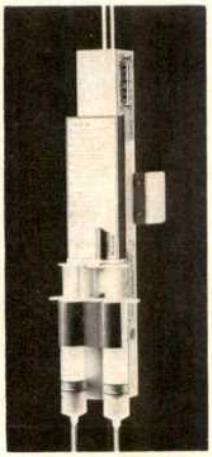

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Published monthly, Annual subscriptions: U.K. £27·50, U.S.A. and Canada U.S.$65, Airmail U.S.$155; Rest of World £33, Airmail £65; (or equivalent in any other currency). ISSN 0007–0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.

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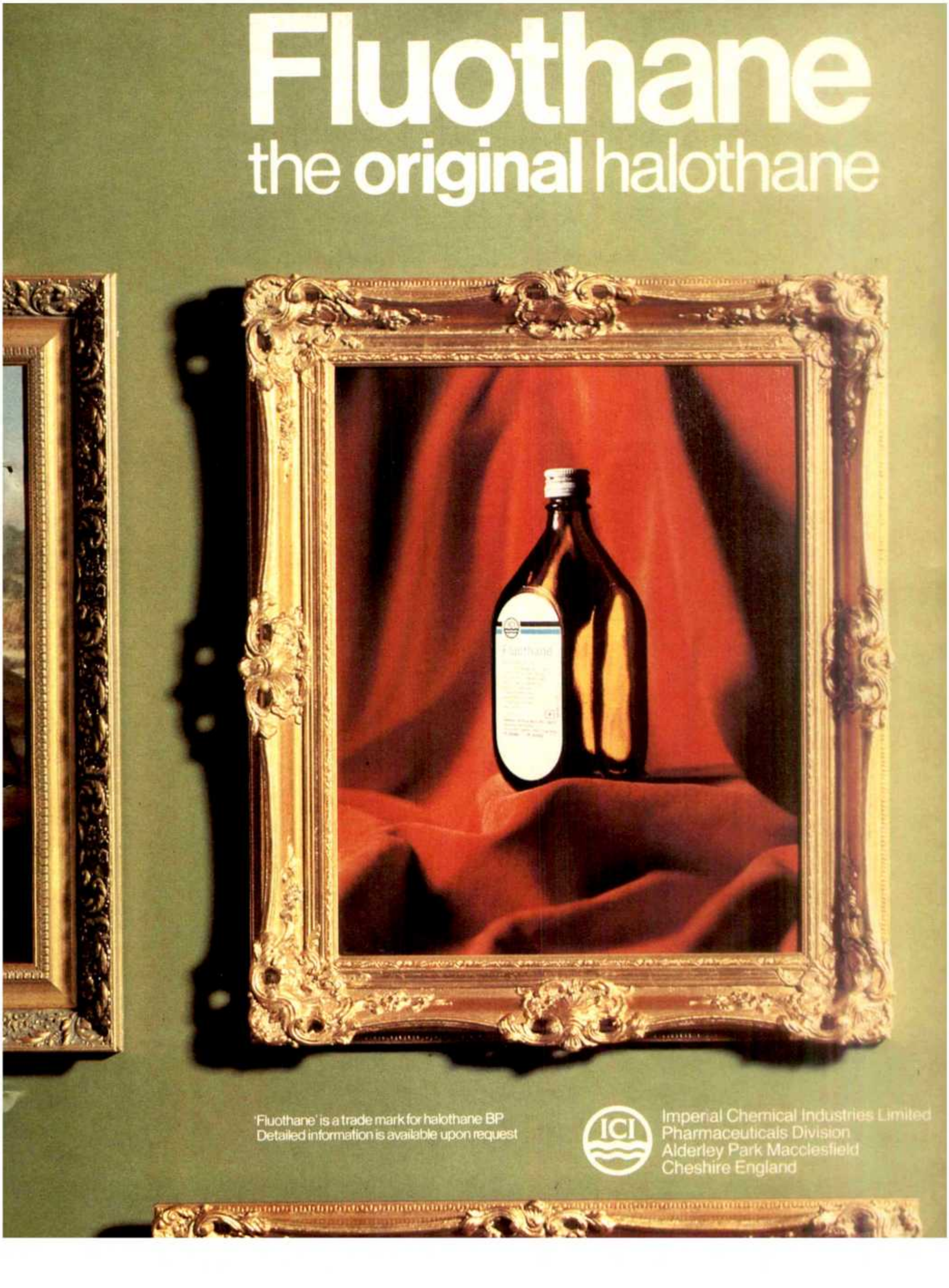

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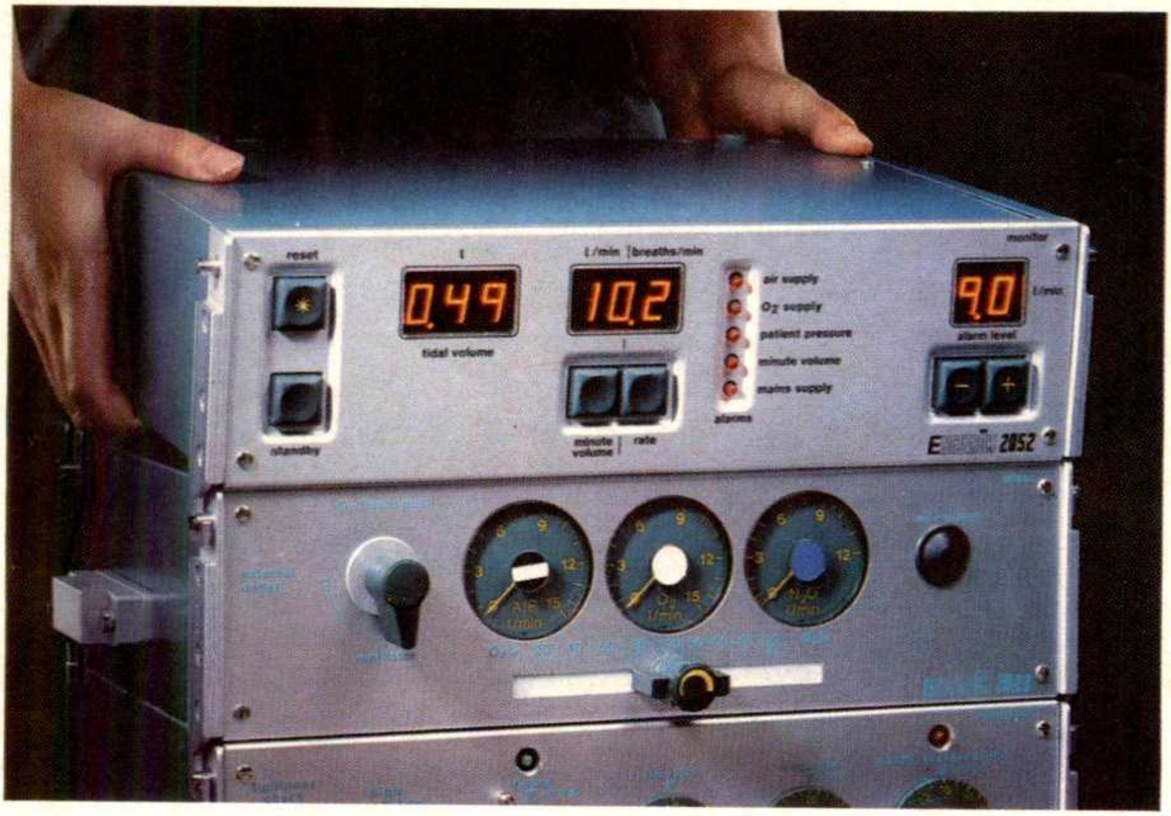

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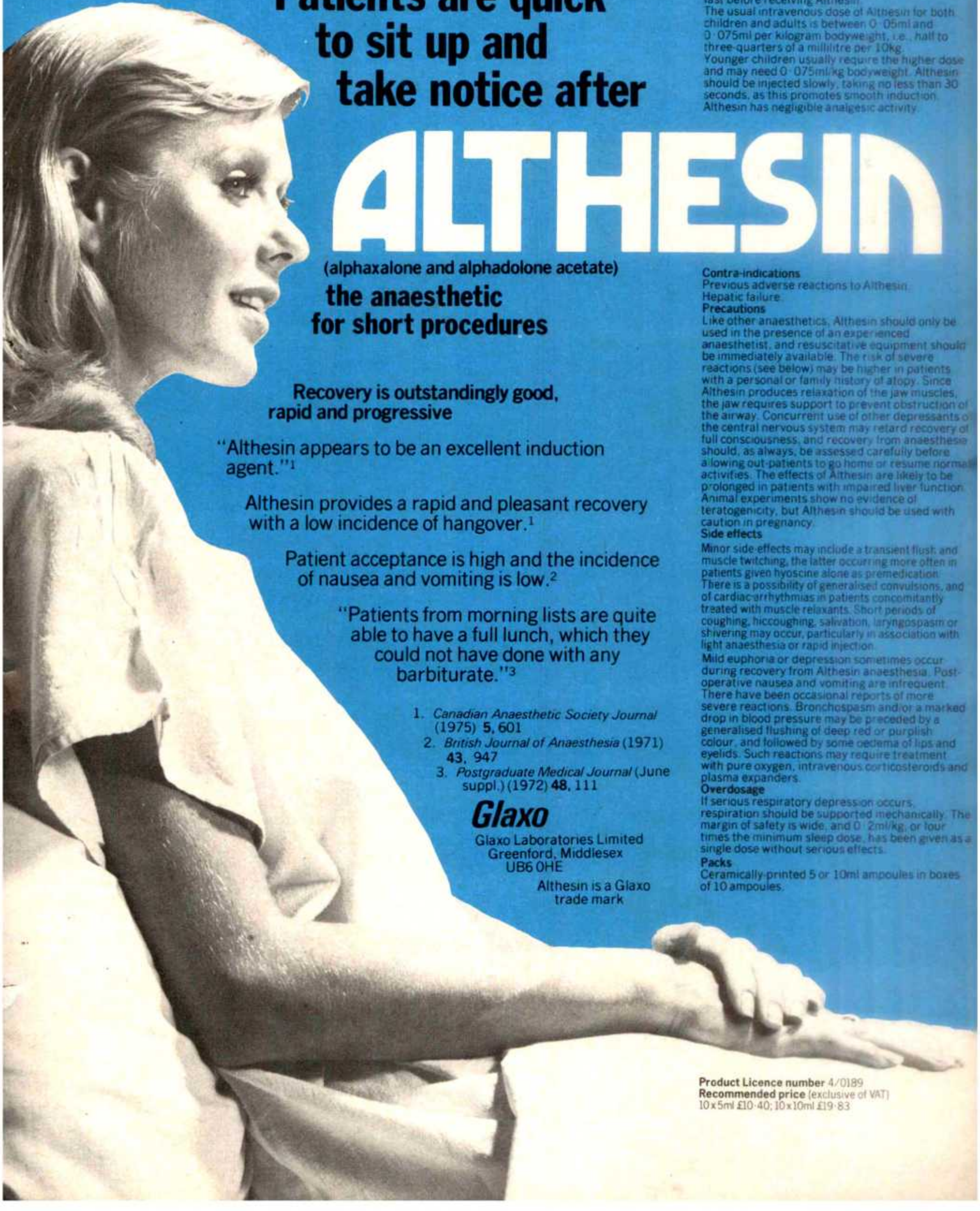
Engström 2000 - the respirator with features that puts it ahead of all others.



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Recovery is outstandingly good, rapid and progressive

"Althesin appears to be an excellent induction agent."[1]

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Patient acceptance is high and the incidence of nausea and vomiting is low.[2]

"Patients from morning lists are quite able to have a full lunch, which they could not have done with any barbiturate."[3]

1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

Glaxo

Glaxo Laboratories Limited
Greenford, Middlesex
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Althesin is a Glaxo trade mark

Prescribing information

Uses

Induction of anaesthesia
Maintenance of anaesthesia
Experience is insufficient at present to advocate use of Althesin in infants under one year, in patients with hepatic dysfunction, and for maintenance of anaesthesia in obstetrics.

Dosage and administration

As usual, it is recommended that patients should fast before receiving Althesin.
The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e., half to three-quarters of a millilitre per 10kg.
Younger children usually require the higher dose and may need 0·075ml/kg bodyweight. Althesin should be injected slowly, taking no less than 30 seconds, as this promotes smooth induction.
Althesin has negligible analgesic activity.

Contra-indications

Previous adverse reactions to Althesin.
Hepatic failure.

Precautions

Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants o the central nervous system may retard recovery of full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume normal activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects

Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, and of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post-operative nausea and vomiting are infrequent. There have been occasional reports of more severe reactions. Bronchospasm and/or a marked drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids and plasma expanders.

Overdosage

If serious respiratory depression occurs, respiration should be supported mechanically. The margin of safety is wide, and 0·2ml/kg, or four times the minimum sleep dose, has been given as a single dose without serious effects.

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Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publishers.

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Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

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Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full addresses) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all of the authors.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

Title page

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should also be suggested.

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The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

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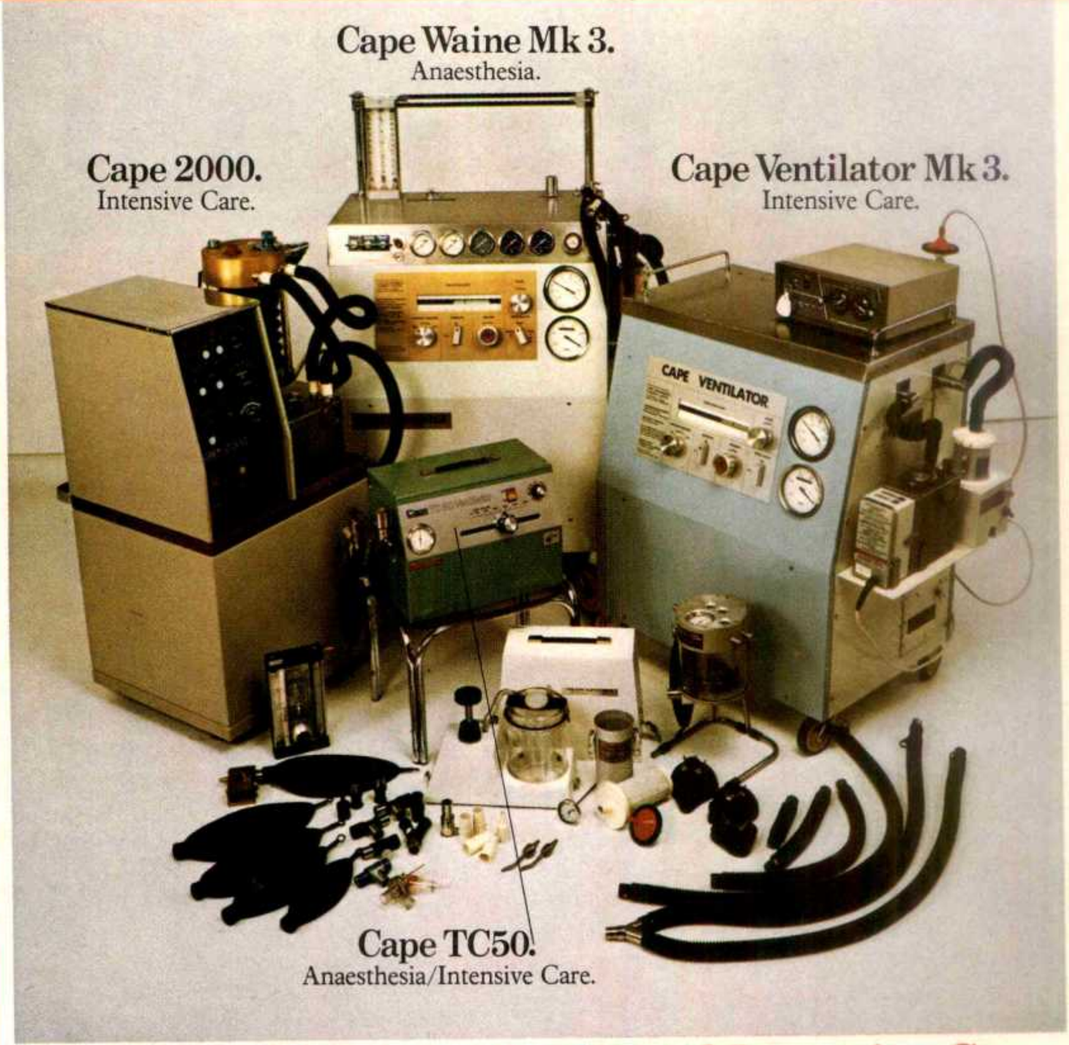

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When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

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Description of experimental results, while concise, should permit repetition of the experiments by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

Discussion

The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

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References

There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

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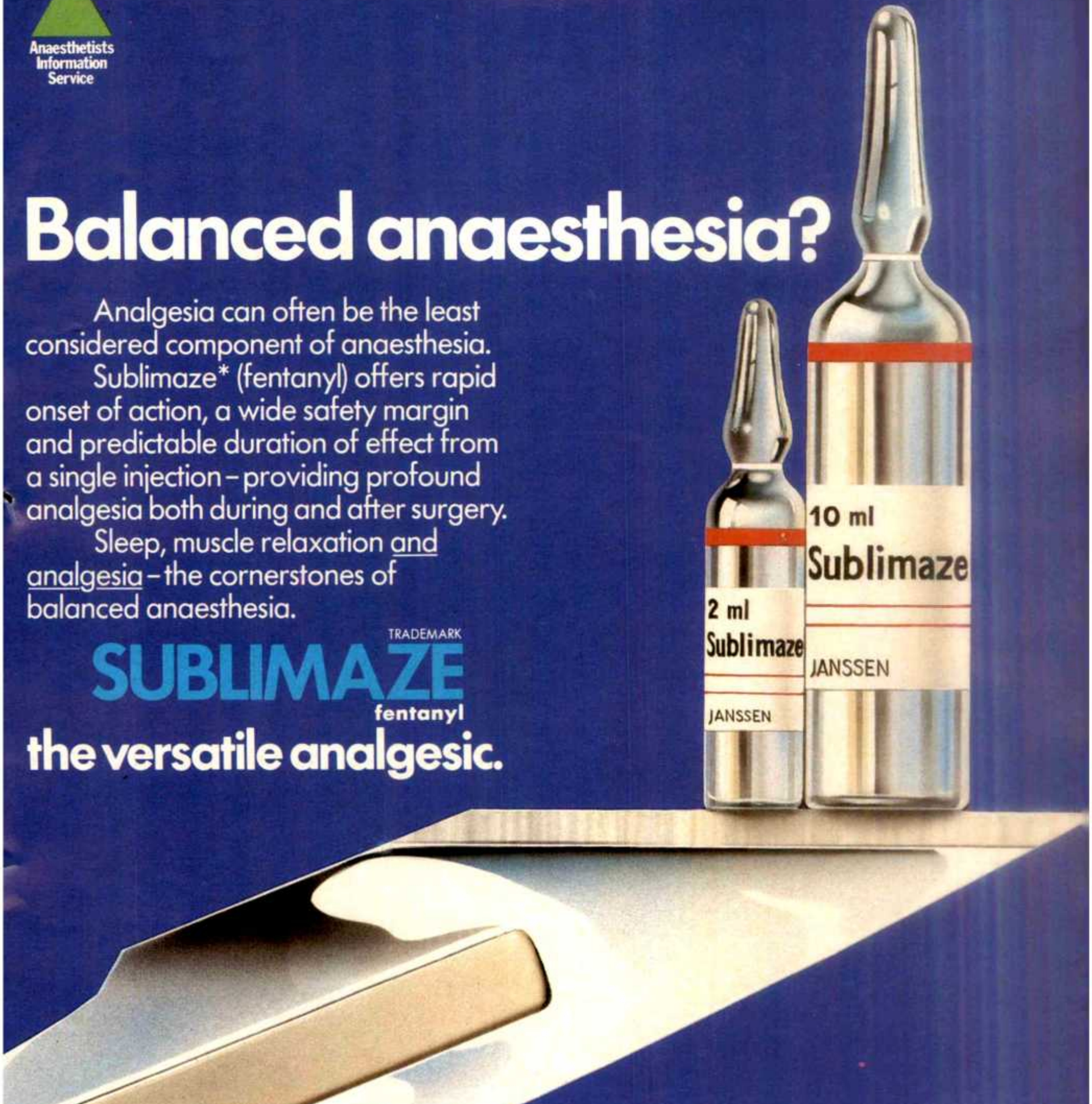

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Contra-indications Respiratory depression; obstructive airways disease. Concurrent administration with MAOIs or within 2 weeks of discontinuation of them.

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2. RESULTS (small capitals)
3. Blood-gas analysis (l.c. roman)
4. *The action of drugs* (italics, centre)
5. *Lung function studies* (italics, full out)
6. *Volume.* Large volumes. . (italics, indent)

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Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

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These should be corrected and returned to the sub-editor *within 48 hours of receipt*. Overseas contributors should return their proofs by airmail.

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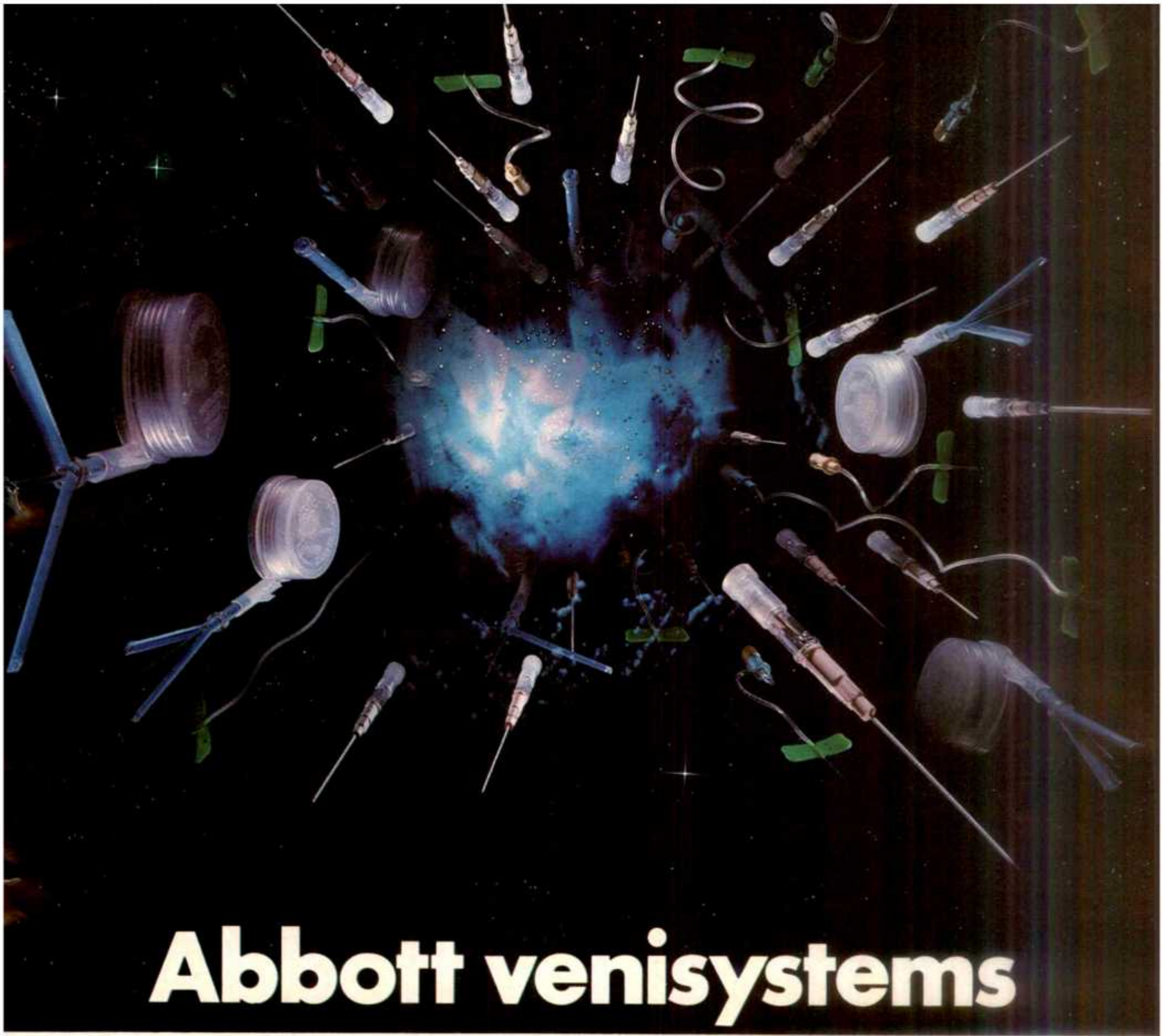

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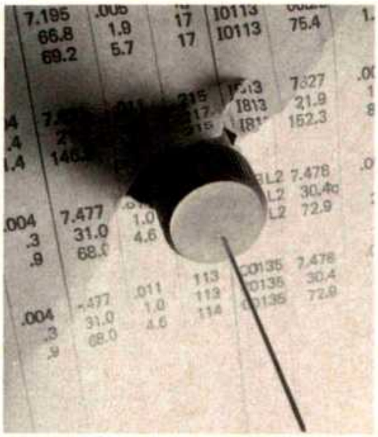

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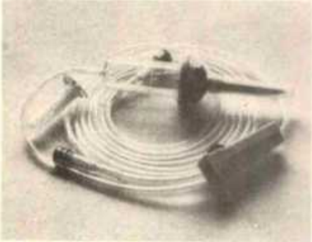

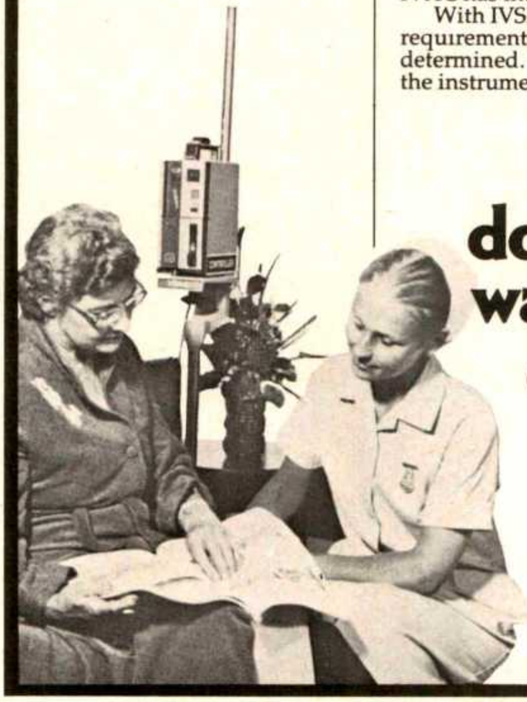

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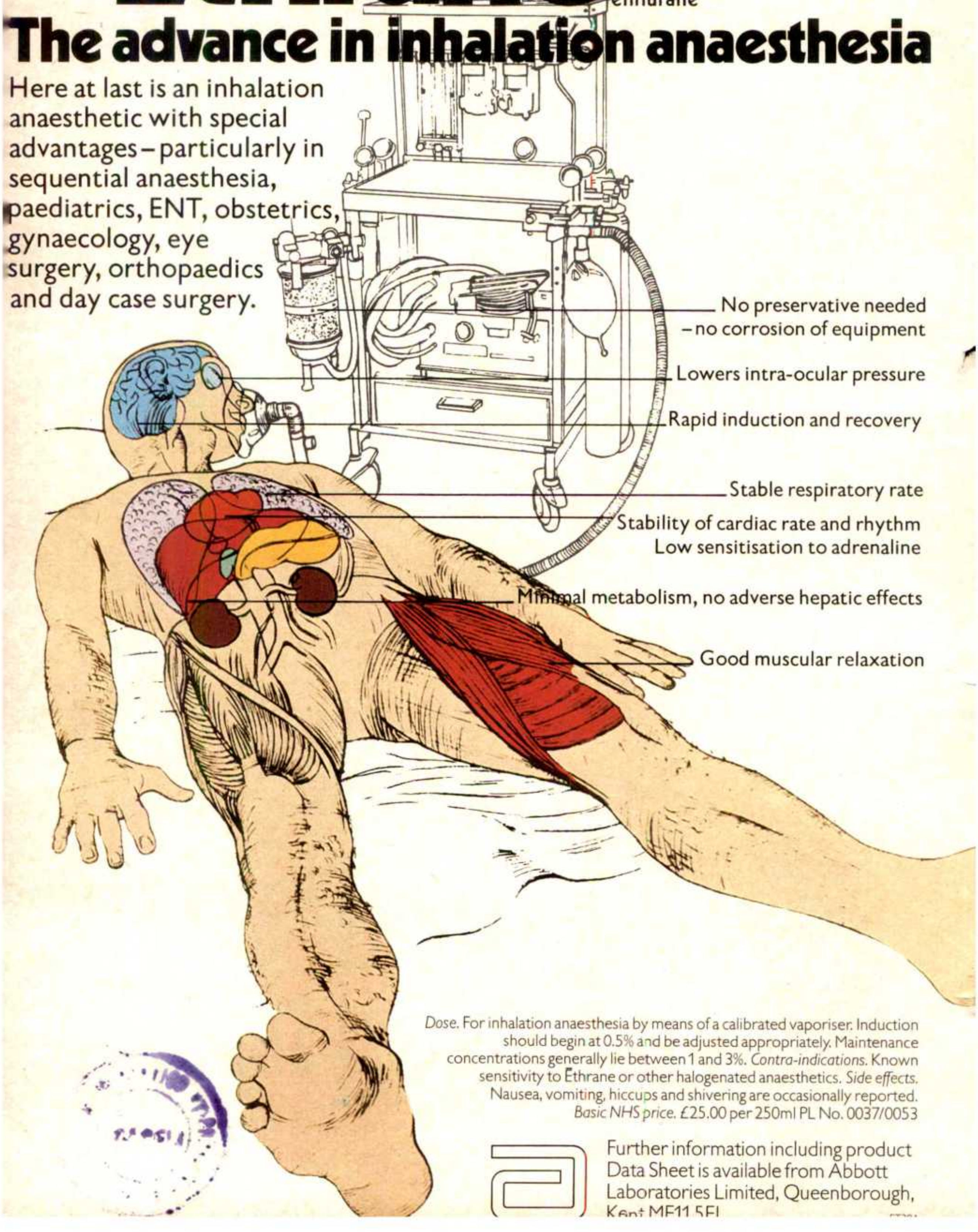

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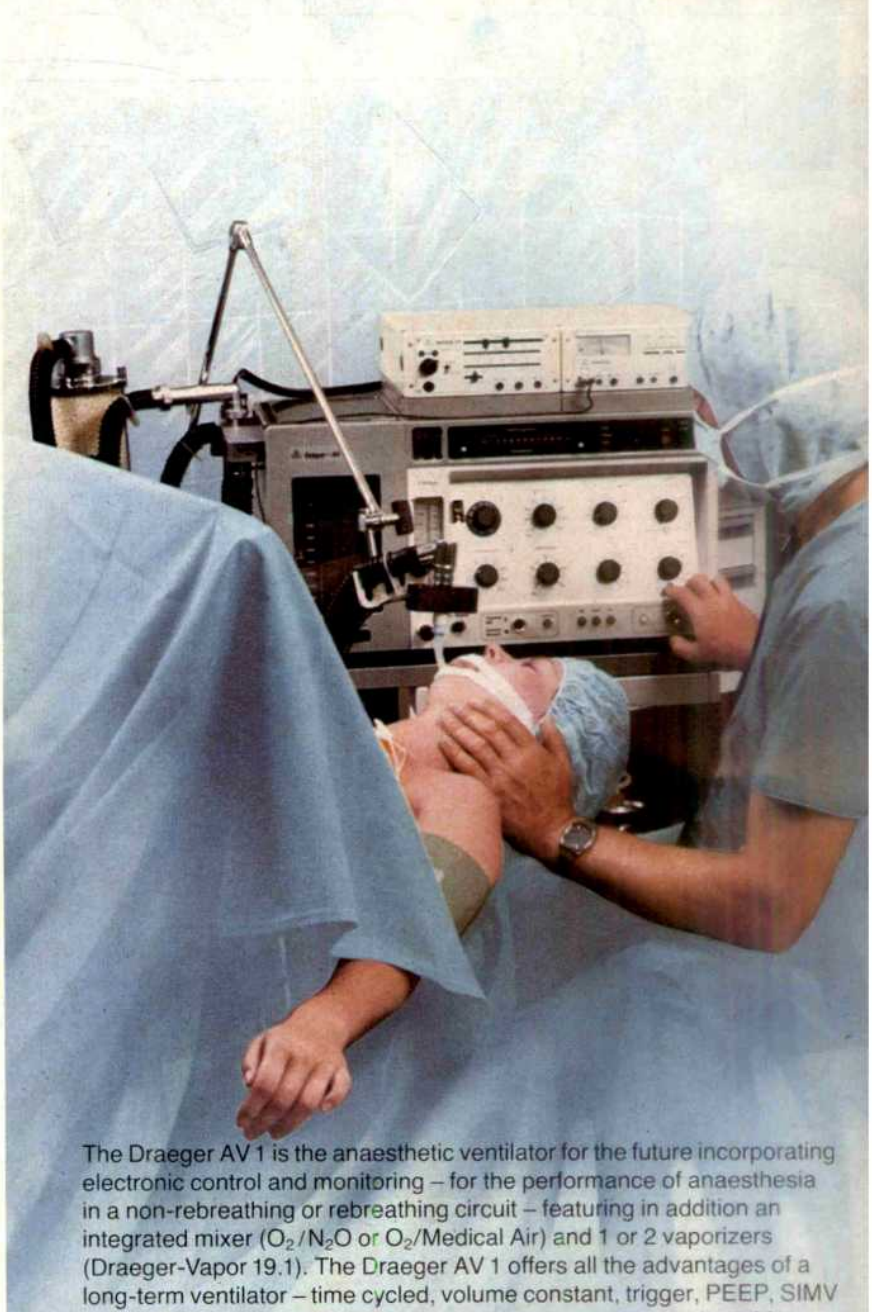

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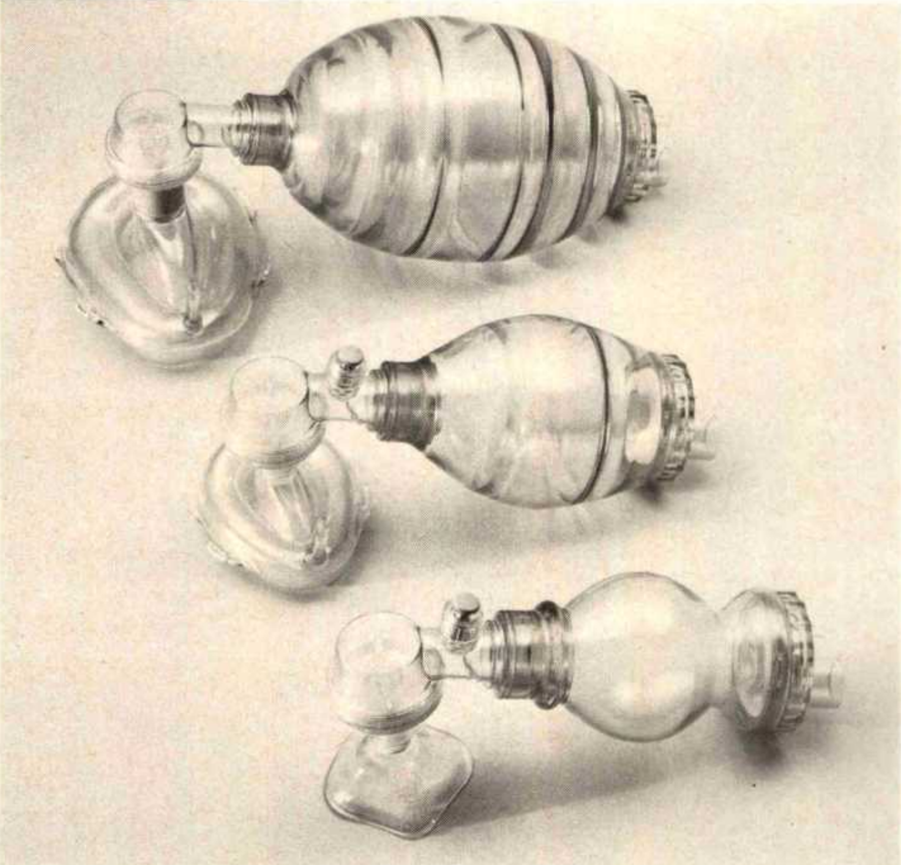

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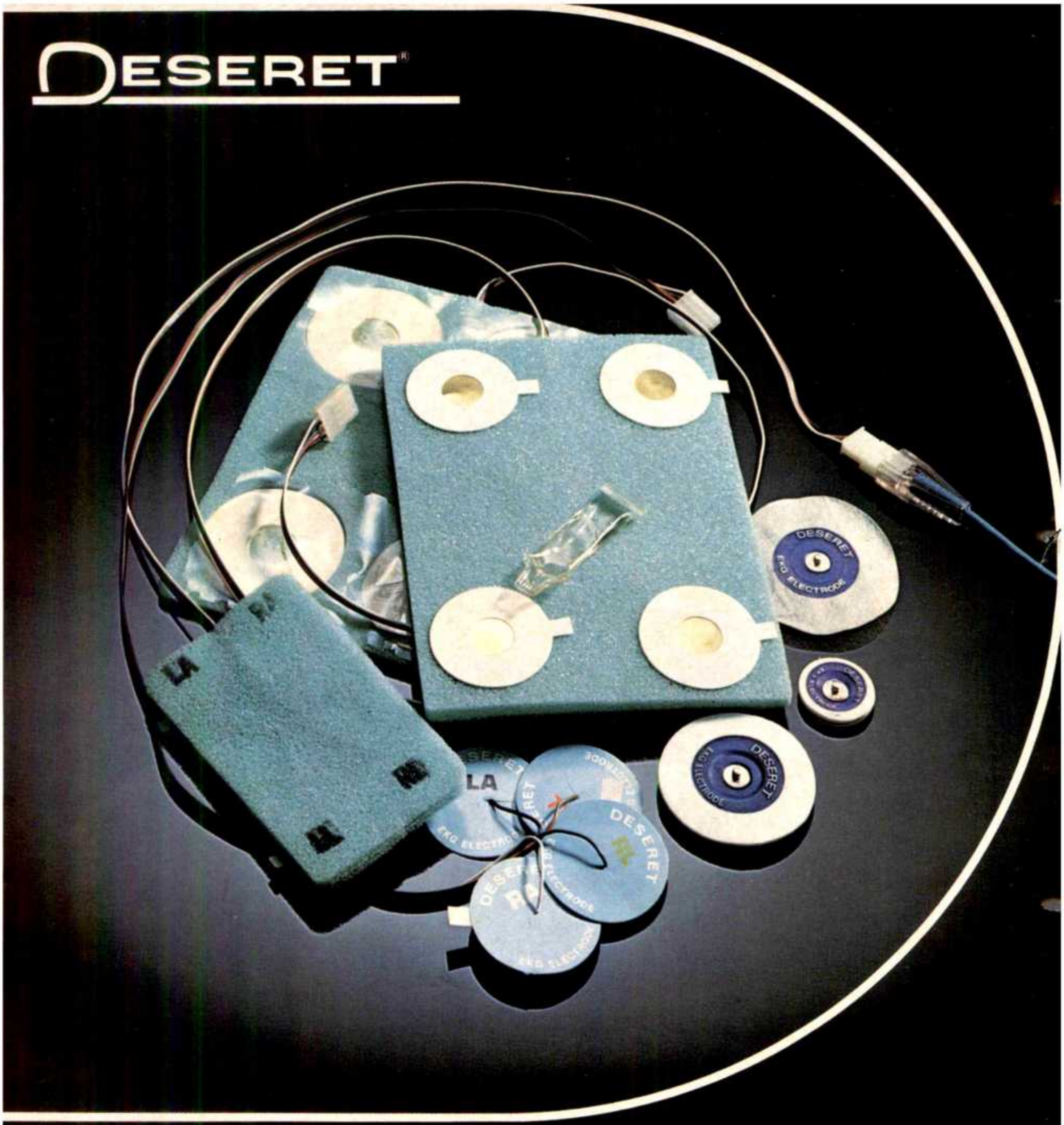

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VOLUME 52, No. 10 OCTOBER 1980

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EDITORIAL

ARE THERE LONG-TERM EFFECTS OF KETAMINE ON THE CENTRAL NERVOUS SYSTEM?

The adverse side-effects of ketamine, including motor and psychic emergence phenomena, have been well documented (Corssen and Domino, 1966; Dundee and Wyant, 1974). However, because of its relatively long duration of action, ease of administration and the stability of the cardiorespiratory systems, it is regarded by some authors as the anaesthetic agent of choice in several clinical conditions, for example in children undergoing radiotherapeutic procedures and for repeated anaesthesia in difficult circumstances such as patients with burns (Gjessing, 1968; Page, Morgan and Loh, 1972; Bennet and Bullimore, 1973). In view of the disturbingly severe hallucinogenic effects which may persist for relatively long periods following a single dose of ketamine (Collier, 1972; Rosenthal, 1964), and the known permanent effects on the brain which may be caused by the long-term administration of various groups of drugs, for example phenothiazines, tricyclic antidepressants and narcotics (Davies, 1977; Pearson and Richter, 1979), the question of potentially permanent adverse effects on the central nervous system as a result of ketamine could be a cause for concern.

There are seven case reports in the literature of prolonged psychic phenomena occurring for periods up to 1 year, following the administration of a single dose, or in one patient two doses, of ketamine and the subject has been reviewed by Steen and Michenfelder (1979). In one patient (Perel and Davidson, 1976) serious symptoms persisted for 5 days, while in three others there were minor disturbances for up to 3 weeks (Fine and Finestone, 1973). In two patients reported by Meyers and Charles (1978), symptoms persisted for up to 1 year, but there were no longer-term effects and both patients had severe congenital brain abnormalities. One 29-yr-old female patient who had received a single dose of ketamine for a minor gynaecological procedure after premedication with Cyclimorph (morphine and cyclizine tartrate) consulted a psychiatrist 1 year later complaining of hallucinations, "passing out spells" and feelings of unreality and hesitation which she attributed to her anaesthetic (Johnson, 1971). A psychiatrist considered that her symptoms were similar to the effects of LSD 25. The possibility that these symptoms could be attributed to the single dose of ketamine administered 1 year previously could not be excluded, but seems unlikely. Unfortunately it has not been possible to obtain information on the subsequent progress of this patient (B. D. Johnson, personal communication).

Albin and others (1970), in a study of 221 adult patients, compared the psychological changes following ketamine anaesthesia with those of other anaesthetics. Psychometric tests were applied repeatedly for periods of more than 1 year after anaesthesia and there were no significant differences between the two groups in terms of mental performance, hallucination and behavioural factors. These authors concluded that the use of ketamine, even after repeated exposures, does not cause long-term impairment of personality or intellectual function.

During a study of the effects of pseudomonas infection in animals, Bree, Feller and Corssen (1967) administered ketamine 25 mg kg^{-1} i.m. to five monkeys on 27 occasions during 3 months. They observed no abnormal behaviour and the animals remained in good health. Manohar, Maxwell and Winters (1972) gave large doses of the drug i.p. to 11 rats daily for periods up to 3 months. They observed abnormal e.e.g. activity which, for 5 days after withdrawal of the drug, showed a progressive increase in epileptiform activity but without any behavioural associations. Unfortunately, observations were not made beyond this time. There were no histological abnormalities demonstrable in the brains of ketamine-treated animals compared with saline-treated controls. This work is, to say the least, inconclusive and it would merit further serious investigation.

Corssen, Oget and Reed (1971) performed a study on a group of 30 volunteers from a prison population. The subjects were randomly allocated to one of three groups. The first group received ketamine, the second group received thiopentone, and the third group acted as a control to assess personality changes caused by a comparable period of imprisonment. Psychological tests (Minnesota Multiphasic Personality Inventory) were applied immediately before and at 1 week, 4 weeks and 6 months after drug administration. They could not establish a difference between the three groups and concluded that ketamine did not cause permanent psychic changes.

Siegel (1978) studied 23 people who had administered ketamine to themselves to alter mood and social attitudes. The group were largely occasional social users of drugs, but they included one subject who claimed to be addicted to ketamine. Ketamine was administered nasally, i.v. and i.m. All the subjects using the parenteral route had used other hallucinogenic drugs, while all the nasal users had concomitant experience with cocaine. Some users complained that long-term effects included "flashbacks", attentional dysfunction and decreased sociability. However, "positive" and "negative" effects of ketamine on mood appeared to be equally divided. Standard psychometric tests used by Siegel did not reveal adverse effects on the function of the central nervous system which could be attributed specifically to ketamine.

It is almost impossible to prove a negative point. However, in spite of the known short-term effects of ketamine, the tentative conclusion which may be drawn from the evidence currently available is that, as used in anaesthetic practice, ketamine is unlikely to cause permanent changes in personality or intellectual function.

T. O. F. Schorn and J. G. Whitwam

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EFFECT OF SODIUM BICARBONATE ON THE KINETICS OF BUPIVACAINE IN I.V. REGIONAL ANAESTHESIA IN DOGS

Y. DONCHIN, A. RAMU, D. OLSHWANG, Z. NEIMAN AND F. MAGORA

SUMMARY

Changes in pH studied *in vitro* affected considerably the distribution of bupivacaine between the erythrocytes and incubation medium: in an acidic medium, the uptake of bupivacaine by erythrocytes was decreased. The acidosis induced *in vivo* in dogs' limbs during i.v. regional anaesthesia (IVRA) with bupivacaine was corrected by injecting sodium bicarbonate into the occluded limb The concentration of bupivacaine in the cephalic vein was measured in dogs under IVRA After removal of the tourniquet, the drug concentration–time relationship showed a biexponential pattern of decline. Injection of sodium bicarbonate into the limb 10 min before the release of the tourniquet suppressed the rate at which the concentration of bupivacaine decreased during the second phase This slower rate of drug release from the tissues may prolong residual analgesia

I.v. regional anaesthesia (IVRA) is useful for operative procedures involving the limbs (Holmes, 1963; Mazze and Dunbar, 1966; Eriksson, 1969; Prithvi Raj et al., 1972). When lignocaine 0.5% in a dose of 3 mg kg^{-1} is used, analgesia regresses within a few minutes after release of tourniquet and severe pain ensues (Holmes, 1963; Watson, Brown and Reich, 1970). However, extension of residual analgesia after release of the tourniquet can be achieved following the administration of bupivacaine (Evans et al., 1974; Magora et al., 1978). Although the duration of the residual analgesia is proportional to the dose of the local anaesthetic agent injected into the limb (Evans et al., 1974), increasing the quantity of the anaesthetic agent may increase the danger of drug toxicity.

The duration of the residual analgesia depends on the ability of the drug to remain in the nerve in quantities sufficient to cause blockade of neural transmission (Evans et al., 1974). The marked acidosis that occurs in the ischaemic limb under IVRA (Déry et al., 1965) may influence the distribution of a weak basic drug such as bupivacaine ($pK_a = 8.1$) between the cells and the extracellular fluid thus affecting the duration of the nerve blockade (Schanker, Nafpliotis and Johnson, 1961; Tucker and Boas, 1971). For example, it has been shown in rabbits that systemic acidosis causes a greater plasma concentration of bupivacaine, thus indicating that at a lower pH less drug penetrates the tissues (Sjöstrand and Widman, 1973).

The influence of pH on the uptake of bupivacaine by erythrocytes was studied *in vitro* to serve as a model for the role of pH in the distribution of the drug between tissue cells and extracellular fluid. In addition, the pH of the ischaemic limb was corrected and its effect on bupivacaine kinetics was investigated in the dog.

MATERIALS AND METHODS

A paediatric pressure cuff was applied to the forelimb above the elbow of six German Shepherd dogs weighing 20–25 kg and under pentobarbitone anaesthesia. A peripheral vein distal to the tourniquet, the cephalic vein proximal to the tourniquet and the contralateral external jugular vein were cannulated. After exsanguination of the limb with an Esmarch rubber bandage, the pressure cuff was inflated to 250 mm Hg, and occlusion was maintained for 20 min. Immediately following inflation of the cuff, bupivacaine (Marcain, Bofors, Sweden) 2 mg kg^{-1} of a 0.5% solution containing ^{3}H-bupivacaine 1–2 mCi (generally labelled; purchased from the Department of Radiochemistry, Nuclear Research Centre, Negev, Israel) was injected into the peripheral vein distal to the tourniquet after which the cannula was flushed

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with 2 ml of saline. In two dogs, 7.5% sodium bicarbonate 10 ml was injected through the same vein 10 min before deflating the tourniquet. Five blood samples (5 ml each) were withdrawn from the cephalic vein during vascular occlusion (dogs showing leakage of bupivacaine were discarded) and at 1, 2, 3, 5, 7, 10, 15, 20, 25, 35, 45, 60, 75, 90 and 120 min after cuff release. Blood samples from the contralateral external jugular vein were taken also. The blood was centrifuged, the plasma separated and stored at −20 °C for further analysis.

Plasma aliquots (in duplicate) were alkalinized and the bupivacaine extracted three times into ethyl acetate (1 : 20 volume ratio). The solvent was evaporated and the residue dissolved in methanol containing non-labelled drug (1%). Aliquots of the methanol extracts were submitted to chromatography on silica gel F_{254} t.l.c. plates, and developed in diethylamine : benzene : cyclohexane (15 : 3 : 2 v/v). The bupivacaine spots were visualized by u.v. light, marked ($R_F = 0.59$), scraped into scintillation vials, mixed with scintillation fluid (Instagel, Packard) and the radioactivity measured by a liquid scintillation spectrometer (Packard TriCarb).

The efficiency of the system was evaluated in control experiments in which plasma was incubated with ^{3}H-bupivacaine. More than 94% of the total plasma radioactivity was recovered from the drug spots on the t.l.c. plates.

In two other dogs, arterial tourniquets were applied to both forelimbs (without exsanguination) for 20 min and 0.5% bupivacaine 2 mg kg^{-1} was injected into a peripheral vein of each limb distal to the tourniquet. Ten minutes after drug administration, 7.5% sodium bicarbonate 10 ml was injected into the vein of one forelimb. The pH was measured (Radiometer ABL-2) in blood samples withdrawn intermittently for 30 min from another peripheral vein of each forelimb.

To study the distribution of bupivacaine in the erythrocytes and incubation media at different pH values, fresh human heparinized blood was centrifuged and the plasma and buffer layers removed. The packed cells were washed three times with isotonic phosphate buffer (pH 7.35) and suspended in an equal volume of isotonic phosphate buffers with the following pH values: 6.8, 7.0, 7.2, 7.4 or 7.6. ^{3}H-Bupivacaine was added to the suspension to a final concentration of 0.5 µg ml^{-1} or 4.0 µg ml^{-1}, and the suspension was incubated at 37 °C in a shaking water bath. Samples were withdrawn at 15, 30 and 60 min. In each sample, the haematocrit (capillary centrifugation) was determined; the remaining part of the sample was centrifuged and the incubation fluid separated and the pH and radioactivity were measured.

To measure the effect of pH on drug efflux from the erythrocytes, washed cell suspensions containing ^{3}H-bupivacaine were incubated at 37 °C for 20 min, after which the cells were transferred to equal volumes of isotonic phosphate buffers having pH values ranging from 6.8 to 7.6 (final drug concentration: 4 µg ml^{-1}) and incubated for a further 20 min. After measuring the sample haematocrit, the erythrocytes were separated by centrifugation and the pH and radioactivity of the supernatants were determined.

The equation:

$$[\mathrm{H}^+]_{\mathrm{medium}}/[\mathrm{H}^+]_{\mathrm{erythrocytes}} = 3.338 - 0.364 \times \mathrm{pH}_{\mathrm{medium}}$$

(Fitzsimons and Sendroy, 1961) was used to calculate the pH of the erythrocytes.

The concentration of bupivacaine (C) in the erythrocytes was calculated by the equation:

$$C_{\mathrm{erythrocytes}} = \frac{C_{\mathrm{suspension}} - C_{\mathrm{medium}} \times (1\text{-haematocrit})}{\text{haematocrit}}$$

RESULTS

Figure 1 shows the drug concentrations as measured in the cephalic vein of one dog after removal of tourniquet. The pattern of bupivacaine release proved to be biexponential. The method of residuals (Gibaldi and Perrier, 1975) was used to analyse the concentration–time relationship, and the following equation was obtained:

$$C_t = 59.8\ \mu\mathrm{g\ ml}^{-1} \times \mathrm{e}^{-0.1474t} + 8.74\ \mu\mathrm{g\ ml}^{-1} \times \mathrm{e}^{-0.0219t}$$

Injection of sodium bicarbonate significantly changed the concentration–time relationship (fig. 1). The equation obtained was:

$$C_t = 21.36\ \mu\mathrm{g\ ml}^{-1} \times \mathrm{e}^{-0.1966t} + 3.31\ \mu\mathrm{g\ ml}^{-1} \times \mathrm{e}^{-0.0093t}$$

The half lives of the first ($T_{\frac{1}{2}}^{\alpha}$) and second ($T_{\frac{1}{2}}^{\beta}$) phases of the decline of the drug concentrations in the cephalic vein after release of the tourniquet were calculated for each dog (table I). As shown in

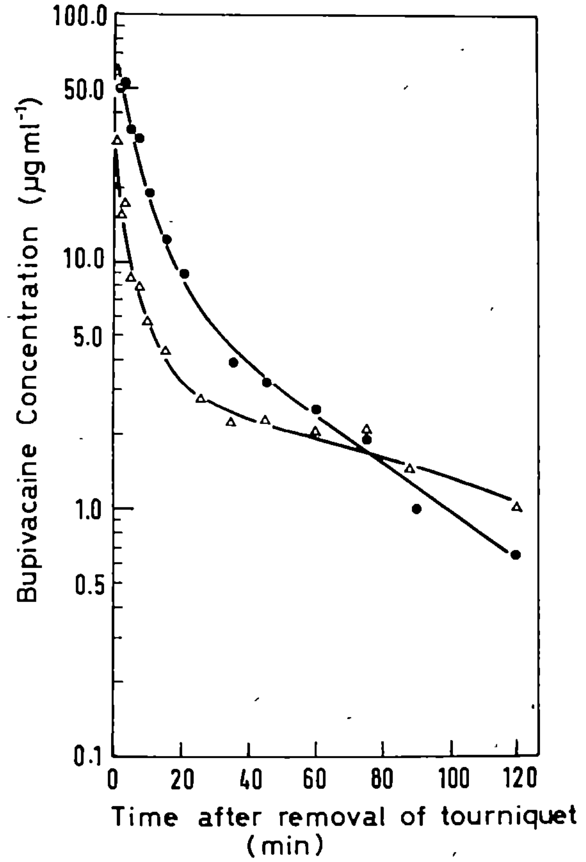

FIG. 1. Plasma concentrations of bupivacaine in the cephalic vein of the treated limb following tourniquet release. ● = control; △ = sodium bicarbonate (injected 10 min before tourniquet release).

TABLE I. *The calculated half lives ($T_{\frac{1}{2}}$) of the first* (α) *and second* (β) *phases of the decrease in the bupivacaine concentration in the cephalic vein after tourniquet release in dogs treated with bupivacaine IVRA.* *r = *correlation coefficient*

Dog No.	Injected with sodium bicarbonate	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)
1	No	4.7 ($r = 0.993$)*	31.6 ($r = 0.991$)
2	No	4.2 ($r = 0.992$)	27.9 ($r = 0.991$)
3	Yes	3.5 ($r = 0.959$)	74.6 ($r = 0.982$)
4	Yes	4.1 ($r = 0.991$)	74.2 ($r = 0.975$)

the table, the initial rate of decrease of the bupivacaine concentration was not affected by the injection of sodium bicarbonate. However, this treatment reduced considerably the rate of drug release during the second phase.

The changes in blood pH in the occluded limb after the injection of sodium bicarbonate were measured in two dogs (table II). It is evident from the table that, immediately after the administration of bupivacaine (a standard Marcain solution of pH 6.0), a marked decrease in the blood pH of the occluded limb occurred. This decrease in pH continued at a slower rate for as long as ischaemia was sustained. The pH returned rapidly to normal values after release of the tourniquet. Injection of sodium bicarbonate caused a sharp increase in blood pH, which lessened during the remaining period of ischaemia.

Irrespective of the pH of the medium, *in vitro* incubation of erythrocytes with ^{3}H-bupivacaine 0.5 μg ml^{-1} for 15 min resulted in an erythrocyte/medium drug concentration ratio which was not significantly different from that obtained after incubation of 1 h. This implies that equilibrium is reached in less than 15 min. There was an inverse relationship at equilibrium between the pH and the drug concentration in the medium (fig. 2A), indicating increased drug uptake by the erythrocytes at greater pH values. The same relationship was found when the concentration of the drug was increased eight-fold (fig. 2B). The erythrocyte/medium bupivacaine concentration ratio as a function of the medium's pH is depicted in figure 3. The final distribution ratio achieved at each pH was independent of the initial drug concentration in the erythrocyte suspension. This dominant role of pH in the distribution of bupivacaine was noted also when the pH of the medium was changed after pre-incubation of the erythrocytes with ^{3}H-bupivacaine (fig. 3).

Assuming that only uncharged drug molecules can cross the erythrocyte membrane, and that the anaesthetic does not bind to erythrocyte constituents, the equation of Jacobs (1940) for weak bases may be used to calculate the distribution of the drug in the *in vitro* system:

$$C_{\text{erythrocytes}}/C_{\text{medium}} = \frac{1 + 10^{(\mathrm{p}K_a - \mathrm{pH}_{\text{erythrocytes}})}}{1 + 10^{(\mathrm{p}K_a - \mathrm{pH}_{\text{medium}})}}$$

The concentration ratios as calculated by Jacobs' equation (fig. 3) proved to be smaller than those obtained from $C_{\text{suspension}}$, C_{medium} and haematocrit data. The difference may represent binding of bupivacaine to the erythrocyte constituents. These differences suggest also that this extra binding of the drug to erythrocytes may be pH dependent.

TABLE II *The effect of the injection of sodium bicarbonate on blood pH changes during IVRA with bupivacaine in dog occluded limb*

Time after application of tourniquet (min)	Venous blood pH			
	Dog 1		Dog 2	
	Right limb	Left limb	Right limb	Left limb
0	7.23	7.23	7.32	7.32
1	7.07	7.06	7.12	7.10
3	7.08	7.03	—	—
5	—	7.04	7.18	7.19
9	7 05	7.03	7.16	7.19
10		Injection of bicarbonate		Injection of bicarbonate
12	7 06	7.57	7.08	7.87
15	7.09	7.57	7.09	7.72
19	6.99	7.38	7.06	7.61
20	Release of tourniquets		Release of tourniquets	
21	7.15	7.15	7.28	7.37
25	7.18	7.15	7.28	7.31
30	—	—	7.29	7.29

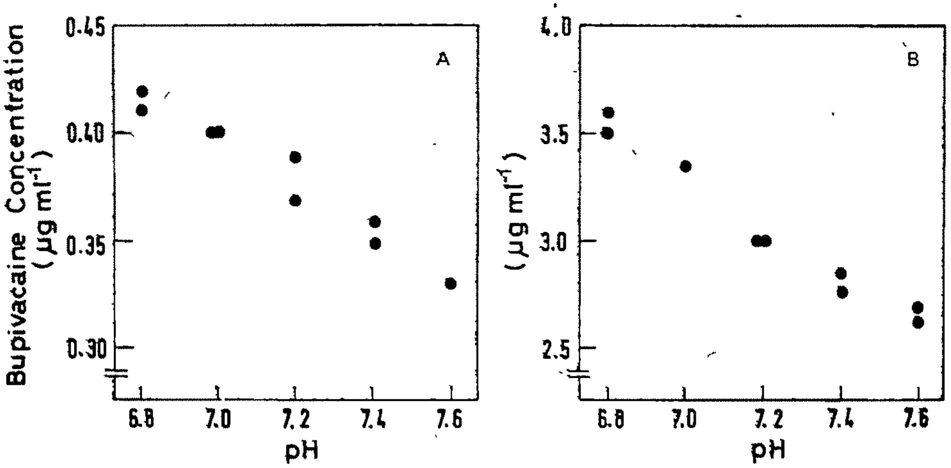

FIG. 2. The concentration of bupivacaine in the medium after 30 min incubation of erythrocytes in media buffered at pH 6.8–7.6. Concentration of ^{3}H-bupivacaine in the cell suspension: A = 0.5 µg ml^{-1}; B = 4 µg ml^{-1}.

DISCUSSION

I.v. regional anaesthesia administered with a standard acidic solution of bupivacaine (Marcain) resulted in an immediate decrease in blood pH in the occluded limb. The pH continued to decrease as long as vascular obstruction was maintained (Déry et al., 1965). A subsequent injection of sodium bicarbonate into the occluded limb brought about an instantaneous and marked restoration of the pH (table II).

The *in vitro* experiments revealed that in suspensions with low pH, the uptake of bupivacaine by the red cells was diminished. The influence exerted by a given pH on the distribution of the drug was not affected by prior incubation at a different pH. This implies that pH *per se* induces

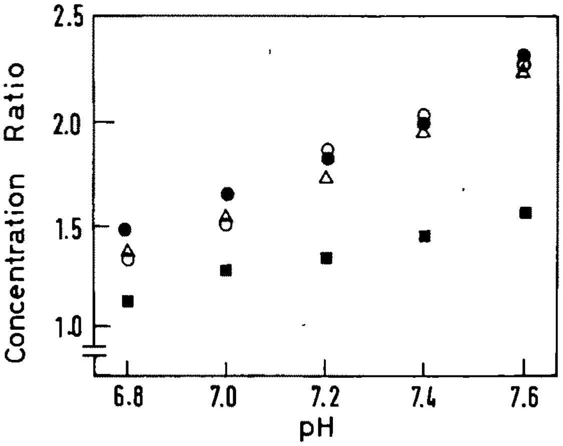

FIG. 3. Erythrocyte/medium bupivacaine concentration ratio as a function of the medium's pH. Erythrocytes were incubated with 0.5 $\mu g\ ml^{-1}$(●) and 4 $\mu g\ ml^{-1}$ (○), or preincubated with 4 $\mu g\ ml^{-1}$ at pH 7.35 (△). The expected ratios calculated from Jacobs' equation are shown (■).

movement of bupivacaine through the cell membrane in both directions, and that the final equilibrium distribution ratio will depend on the pH differential across the cell membrane. Thus, correcting the acidosis in the ischaemic limb may influence considerably the distribution of bupivacaine between tissue cells and extracellular fluid.

The concentration of bupivacaine in the cephalic vein of the dog after the release of the tourniquet declined in a biexponential pattern, as reported by others (Tucker and Boas, 1971; Evans et al., 1974). Drummond (1975) showed that, on release of a 20-min arterial occlusion, the initially increased blood flow in the limb returned to normal values within 5 min. The hyperaemic response was reduced markedly by administration of bupivacaine.

In the present study, the initial rapid release of bupivacaine extended beyond 20 min. Therefore, the hyperaemic response occurring after the release of the tourniquet cannot explain fully the initial phase of the drug liberation. It is suggested that the first phase represents washout of the drug still remaining in the venous system and adjacent tissue spaces, while the second (slower) phase of discharge of the drug from the limb is controlled mainly by the rate of efflux of the drug from the cells. Sodium bicarbonate, injected directly into the occluded limb, arrested the rate of release during the second phase of the clearance of bupivacaine, while it had no effect upon the first (rapid) phase (table I). In view of the influence of pH on the uptake of bupivacaine into the cells *in vitro* and the effect of sodium bicarbonate on the biexponential pattern of drug release *in vivo*, it is feasible that the second (slow) phase is indeed governed by the rate of drug efflux from the cells.

The concentration of drug measured initially in the cephalic vein was lower in bicarbonate-treated dogs. This may have been a result of dilution of the residual anaesthetic in the intravascular bed by the bicarbonate solution.

The toxicity of local anaesthetic agents depends upon their concentration in the blood (Foldes et al., 1960; Bromage and Robson, 1961; Foldes et al., 1965). With the IVRA technique, peak arterial concentrations of the drug are present within a few minutes of the release of the tourniquet (Eriksson, 1969). Only the initial washout of the drug is important in respect of toxicity, since in the second phase of drug release the amounts of the anaesthetic agent discharged from the limb are too small to produce toxic arterial blood concentrations. The injection of sodium bicarbonate slows even further the release of bupivacaine during the second phase and would therefore not be conducive to drug toxicity.

On the other hand, since the residual analgesia continues far beyond the end of the initial phase of the release of bupivacaine (Evans et al., 1974), its extent may be related to the rate of the drug discharge from the limb during the second phase. Therefore, it is suggested that the sodium bicarbonate induced a slow-down of the release of bupivacaine during the second phase to less than half its control values, and may enhance anaesthesia during IVRA with this drug and may extend the period of residual analgesia. This assumption is currently being investigated in man.

ACKNOWLEDGEMENTS

The authors wish to thank Dr E. Levinger, Department of Clinical Oncology and Radiotherapy, Hadassah University Hospital, for his valuable advice and help with the preparation of the radioactive material, and Mr Y. Sadovsky and Mr D Frenkel for excellent technical assistance. This study was supported in part by a grant from AB Bofors Nobel Kemi, Bofors, Sweden.

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EFFET DU BICARBONATE DE SOUDE SUR LA CINETIQUE DE LA BUPIVACAINE DANS L'ANESTHESIE LOCALE INTRAVEINEUSE CHEZ LES CHIENS

RESUME

Les variations du pH étudiées *in vitro* ont affecté d'une manière considérable la répartition de la bupivacaine entre les érythrocytes et le milieu d'incubation; dans un milieu acide, la fixation de la bupivacaine par les érythrocytes s'est trouvée réduite. L'acidose induite *in vivo* sur des membres de chiens pendant une anesthésie locale intraveineuse (IVRA) à l'aide de bupivacaine a pu être corrigée par l'injection de bicarbonate de soude dans le membre obstrué. La concentration de bupivacaïne dans la veine céphalique a été mesurée sur des chiens soumis à une IVRA. Après retrait du tourniquet, la relation concentration/temps du médicament a suivi un modèle biexponentiel de diminution. L'injection de bicarbonate de soude dans le membre, 10 min avant de relâcher le tourniquet, a supprimé le rythme auquel la concentration de bupivacaïne a dimnué dans le courant de la seconde phase. Ce rythme plus lent auquel le médicament se dégage des tissus peut prolonger l'analgésie résiduelle.

WIRKUNG VON NATRIUM BICARBONICUM AUF DIE AKTION VON BUPIVACAIN BEI INTRAVENÖSER LOKALANÄSTHESIE IN HUNDEN

ZUSAMMENFASSUNG

In vitro untersuchte Veranderungen von pH beeinflussten die Verteilung von Bupivacain zwischen den Erythrozyten und dem Inkubationsmedium; in einem sauren Medium wurde die Aufnahme der Droge durch die Erythrozyten verringert. Die *in vivo* in den Gliedmassen von Hunden hervorgerufene Azidose während intravenöser Lokalanasthesie (IVRA) mit Bupivacain wurde durch eine Injektion von Natrium Bicarbonicum in das angestaute Glied korrigiert. Die Konzentration der Droge in der Kopfvene wurde bei Hunden unter IVRA gemessen, wo nach Knebelentfernung das Verhaltnis zwischen Drogenkonzentration und Zeit einen biexponentiellen Abstieg zeigte. Injektionen von Natrium bicarbonicum in das Glied 10 Minuten vor Lösung des Knebels verringerte die Geschwindigkeit, mit der sich die Bupivacainkonzentration während der zweiten Phase verringerte. Diese langsamere Geschwindigkeit der Drogenausscheidung aus dem Gewebe könnte eine schmerzlindernde Restwirkung verlangern.

EFECTO DEL BICARBONATO SODICO SOBRE LAS CARACTERISTICAS CINETICAS DE LA BUPIVACAINA EN LA ANESTESIA INTRAVENOSA LOCAL EFECTUADA EN PERROS

SUMARIO

Los cambios en el valor del pH estudiado *in vitro* afectaron considerablemente a la distribución de bupivacaína entre los eritrocitos y el medio de incubación: La absorción de bupivacaína por parte de los eritrocitos disminuyó en el medio ácido. El carácter ácido inducido *in vivo* en las extremidades de los perros mediante la bupivacaína, durante la anestesia regional intravenosa (ARIV), se corrigió inyectando bicarbonato sódico en la extremidad pertinente. La concentración de bupivacaína en la vena cefálica se midió en perros sometidos a ARIV. Después de retirar el torniquete, la relación entre concentración y tiempo de la droga, mostró un carácter biexponencial descendente. La inyección de bicarbonato sódico en la extremidad, diez minutos antes de retirarse el torniquete, suprimió el ritmo de disminución de la concentración de bupivacaína durante la segunda fase. Este ritmo más lento de liberación de la droga por parte de los tejidos puede que prolonge la analgesia residual.

Br. J. Anaesth. (1980), 52, 975

NEONATAL THYROID FUNCTION AND ANAESTHESIA*

S. Halevy, M. Liu-Barnett and P. L. Ross

SUMMARY

Thyroid function in the neonate and its response to hexobarbitone anaesthesia were studied in newborn Wistar rats between 24 h and 42 days old. ^{14}C-labelled mixed with unlabelled hexobarbitone was injected i.p. in anaesthetic concentrations. Serum T3, reverse T3 (rT3) and T4 and serum and whole brain hexobarbitone concentrations were measured on wakening. A decrease in serum T3 and rT3 and an increase in T4 concentrations were observed after hexobarbitone at 21 and 30 days. This appears to be a critical period in the neonatal rat. A significant negative correlation was found between the changes in serum thyroid hormone concentrations and whole-brain concentrations of hexobarbitone in 30-day-old male rats. It is suggested that similar effects may occur in the human fetus or neonate subjected to anaesthesia.

Changes in thyroid physiology of profound biological significance occur in the perinatal period of most species, including man. Thyroid hormones play an important role in the perinatal period. Among other functions, they are involved in fetal growth and development, the maturation of the central nervous system—and, possibly, of the lung—and non-shivering thermogenesis.

The most important changes of clinical significance in thyroid physiology in the mother during pregnancy are: the secretion by the placenta of a thyrotrophin; increased synthesis of thyroxine-binding globulin (TGB) by the liver, which is caused by oestrogens under the influence of the placental chorionic gonadotrophin; and relatively small concentrations of free L-3,3′,5-triiodothyronine (T3) and normal free thyroxine (T4), the two forms of thyroid hormone active at cellular level (Selenkow, Birnbaum and Hollander, 1973).

The human fetus and the fetuses of other mammals have small T3 concentrations and very high concentrations of L-3,3′,5′-triiodothyronine or reverse T3 (rT3). The biological significance of the newly identified thyroid hormone, rT3, is uncertain. This is important since most of T3 and rT3 is derived from the peripheral monodeiodination of T4 by the liver and the kidney. Two separate enzymatic processes produce these hormones and these are altered in the fetus (Chopra, Sack and Fisher, 1975; Fisher, 1975; Fisher and Sack, 1975). Between 20 and 30 weeks of gestation the thyroid function of the fetus changes from hypothyroid to almost euthyroid activity. However, thyroid development is complete in humans and the rat at 3–5 weeks after birth. There is a sudden increase in neonatal thyrotrophin (TSH) at birth. As a consequence, there is an increase to greater than normal in both T4 and T3 during the first 24–36 h of life, followed by a gradual decrease towards normal adult values.

In a study of the effect of regional and general anaesthesia on serum thyroid hormones of pregnant women undergoing Caesarean section (Halevy et al., 1978), we found no significant change in serum TSH, but T3 decreased with both anaesthetic techniques. T4 and rT3 showed different changes according to time of sampling or method of anaesthesia.

These findings confirmed data from the literature showing that anaesthetics influence thyroid function in adults (Halevy, 1980). We suggested that anaesthesia may have a greater effect on thyroid function in the hypothyroid newborn, exposed to anaesthetics either before birth or in the first few weeks after birth.

We have now studied the newborn rat as the model for neonatal hypothyroidism. In contrast to most other species, thyroid maturation in the rat occurs late following a period of approximately 3

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* Preliminary results of this study were presented at the 63rd Annual Meeting of the Federation of American Societies for Experimental Biology in Dallas, Texas, April 1–10, 1979.

0007-0912/80/100975-06 $01.00

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weeks of hypothyroidism (Dussault, 1975). We selected hexobarbitone as the anaesthetic since it is an oxybarbiturate which would not interfere with thyroid metabolism.

METHODS

Pregnant Wistar albino rats were obtained from Royalhart Laboratory Animals, Inc., New Hampton, N.Y. and kept for several days to permit acclimatization. A number of animals of the same strain and source were mated in our laboratory. Parturition occurred after 22 days of pregnancy. All adults were kept under identical laboratory conditions: free access to Purina rodent laboratory diet and water; 12 h of light (07.00–19.00 h) and 12 h of darkness and controlled temperature.

A mixture of ^{14}C-labelled and unlabelled hexobarbitone was injected i.p. in doses between 10 and 60 mg kg^{-1}, depending upon the age of the animal, to produce anaesthesia, determined by loss of righting reflex. The duration of sleep was recorded. DL-Hexobarbitone-N-methyl-2-^{14}C, specific activity 1.23 mCi mmol^{-1} was purchased from New England Nuclear, Boston, Massachusetts. The purity of the hexobarbitone was established by thin layer chromatography. The animals were sacrificed on wakening (return of the righting reflex), by cervical dislocation, between 10.00 and 12.00 h. The blood and whole brain were removed and the serum separated. Serum thyroid hormones were measured in controls and following the administration of hexobarbitone, in newborn rats of both sexes at 24, 48, and 72 h, and 7, 14, 21, 30 and 42 days from birth.

T4, T3, and rT3 were determined in the serum of litters or individuals, depending upon the size of the sample, by radioimmunoassay using the commercially available kits. The T4 and T3 kits were obtained from Diagnostic Products Corporation, Los Angeles, California and the rT3 kit from Serono Laboratories, Inc., Braintree, Massachusetts. These kits used ^{125}I-labelled antigen, 8-anilino-1-naphthalene sulphonic acid and goat anti-rabbit gamma globulin.

Hexobarbitone concentrations in either serum or whole brain were measured 14, 21, 30 and 42 days after birth by a modification of the technique described by Kupfer and Rosenfeld (1973) for the quantitation of hexobarbitone or its metabolites. Briefly, hexobarbitone was extracted with 1-chlorobutane followed by another extraction of possible metabolites with ethyl acetate. Subsequently, hexobarbitone was determined by liquid scintillation spectrometry. The efficiency and specificity of unmetabolized hexobarbitone extraction from serum and brain by this method was established *in vitro* by liquid scintillation counting and 85–95% of the added radioactivity was recovered in 1-chlorobutane extracts.

Student's *t* test for unpaired values was performed using 5% as the level of statistical significance.

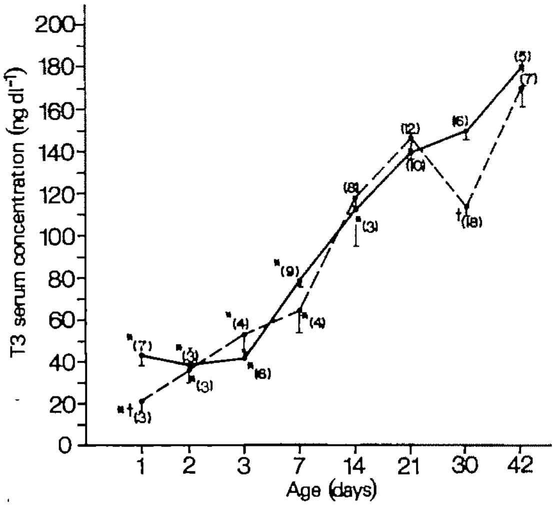

FIG. 1. Serum concentrations of triiodothyronine (T3) (mean ± SEM) in controls (●——●) and hexobarbitone-treated (●- - -●) newborn rats. * = litters; other points = individuals. Numbers of animals in parentheses. †Significantly different from controls.

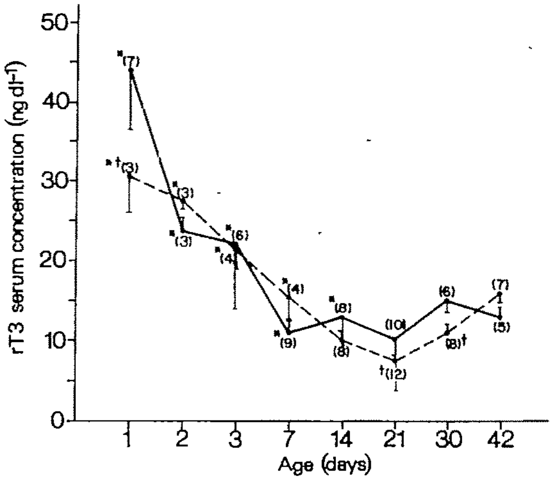

FIG. 2. Serum concentrations of reverse triiodothyronine (rT3) (mean ± SEM) in controls and hexobarbitone-treated newborn rats. (Symbols as in figure 1.)

RESULTS

Serum concentrations of T4, T3 and rT3 in control and newborn hexobarbitone-treated rats are shown in figures 1–3. Except for the first 24 h of life, the most significant changes in T4 and T3, after hexobarbitone anaesthesia, occurred at 21

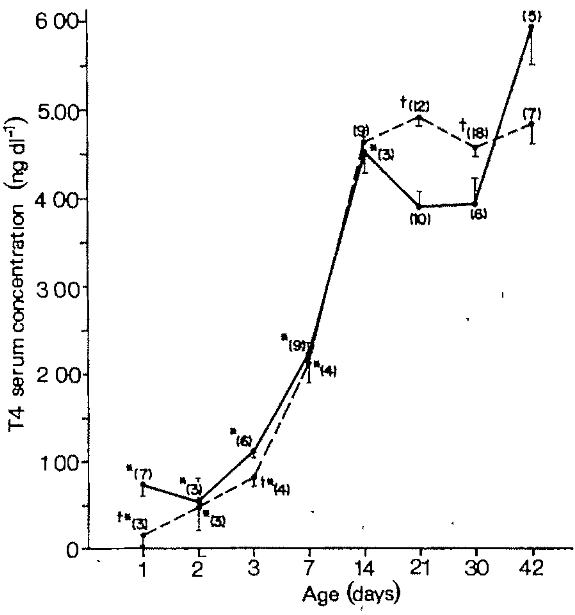

FIG. 3. Serum concentrations of thyroxine (T4) (mean ± SEM) in controls and hexobarbitone-treated newborn rats. (Symbols as in figure 1.)

and 30 days of age. Serum concentration of T4 was increased after the administration of hexobarbitone, whereas that of T3 was decreased. No significant differences were noted between the sexes.

To determine the duration of these changes, we measured serum thyroid hormones at 24 and 72 h after the administration of hexobarbitone to 30-day-old rats of either sex and compared these data with that of the controls and 42-day-old rats. We found significant differences only on recovery from anaesthesia, but no differences at 24 or 72 h after administration of hexobarbitone, although the serum concentrations of T3 were still less than control (fig. 4). Furthermore, in 72 h samples, serum concentrations of the thyroid hormone were similar to those found in 42-day-old rats. Thus the duration of the reported changes is probably limited to the 24-h period in animals exhibiting maximum alterations in serum hormone concentrations.

We analysed the relationship between serum or whole brain concentrations of hexobarbitone and serum thyroid hormones during the period of maximum response to anaesthesia. There was a significant negative correlation between whole brain concentrations of hexobarbitone and serum T4 and T3 in 30-day-old male newborn rats (figs 5 and 6). However, the serum T4 and T3

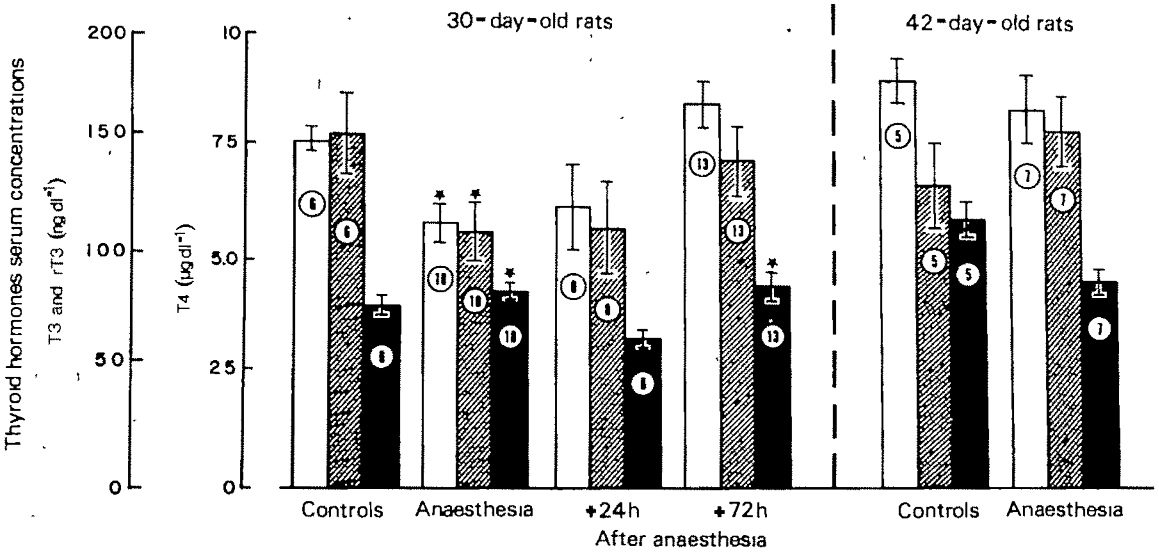

FIG. 4. Serum concentrations of thyroid hormones (mean ± SEM) in controls and hexobarbitone-treated, 30-day-old (wakening, +24 h and +72 h) and 42-day-old rats. Open columns = T3; cross-hatched columns = rT3; black columns = T4. *Significantly different from control. Number of animals in circles.

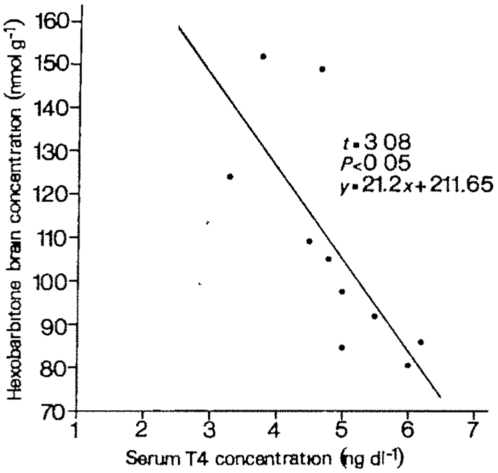

FIG. 5. Relationship between whole-brain concentration of hexobarbitone and serum concentration of thyroxine (T4) in 30-day-old male rat.

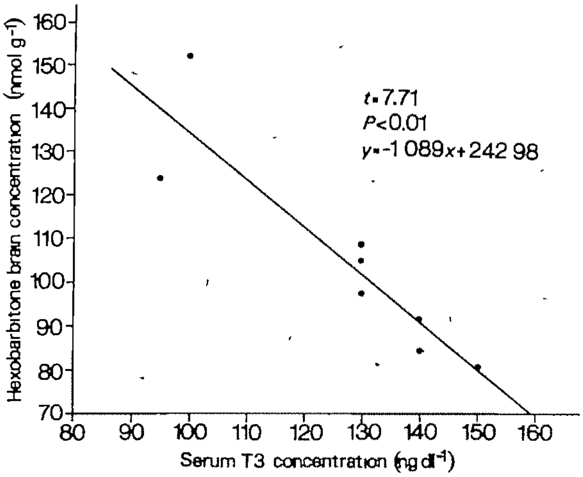

FIG. 6. Relationship between whole-brain concentration of hexobarbitone and serum concentration of triiodothyronine (T3) in 30-day-old male rat.

concentrations exhibited opposite responses to anaesthesia at 21 and 30 days.

DISCUSSION

A number of physical and environmental stresses or external influences, including drugs, may reduce serum T3 concentrations, possibly by inhibition of peripheral monodeiodination of T4, which is the main source after birth (Chopra et al., 1975; Fisher, 1977). The influence of anaesthesia on thyroid function in the neonate at the time of birth has not been investigated although neonatal hypothyroidism is reported to occur with a frequency of approximately 1 in 4000 live births (La Franchi, 1979). Although our results show significant differences in the serum thyroid hormones after anaesthesia with hexobarbitone at 24 h of age, the next significant changes occurred at 21 and 30 days of age only. This was surprising since we suspected that the neonate's thyroid function would be susceptible to anaesthetics throughout the entire hypothyroid period, that is before 21 or 30 days of age. Nevertheless, this study demonstrates that anaesthesia influences the thyroid function of the neonate; that triiodothyronine, the most important metabolically active thyroid hormone decreases after hexobarbitone anaesthesia—an observation which may have clinical significance; that for a limited but specific period the changes in neonatal serum thyroid hormones following administration of hexobarbitone are dependent on sleeping time and the amount of anaesthetic present in the serum or the brain (table I); and that there is a critical period of maximum changes in these hormones around the 30th day after birth in the rat.

The following support these conclusions. It was found that between 14 and 30 days of age, for the *same dose* of anaesthetic, sleeping time decreased dramatically while the serum and brain concentrations of hexobarbitone on wakening increased progressively. Despite this, serum to brain anaesthetic ratios remained almost unchanged and the expected sex differences in anaesthetic response caused by hormonally-induced changes in drug metabolism (Quinn, Axelrod and Brodie, 1958; Eriksson and Yaffe, 1973; Halevy, 1979) were insignificant during this period. However, male animals showed a significant correlation between the brain concentration of anaesthetic and serum T4 and T3 concentrations. This suggests that there may be competition between the anaesthetic and thyroid hormones at least in certain target organs. These changes were of relatively short duration (approximately 24 h) in the 30-day-old rat. However, the most significant change was a decrease in serum T3, the active thyroid hormone at cellular level.

Our experiments show that the observed differences in serum thyroid hormones in the developing rat are caused, at least in part, by anaesthesia. It is possible that there are additional environmental, metabolic or hormonal factors interfering with peripheral T4 metabolism re-

TABLE I. *Sleeping time, serum and brain drug concentrations (mean ± SEM) following hexobarbitone (H) 60 mg kg^{-1} i.p. injection in the newborn rat at 14, 21 and 30 days of age*

Age (days)	Sex	*n*	Sleeping time (min)	Serum H (nmol ml^{-1})	Brain H (nmol g^{-1})
14	M	11	133.6±0.59	126.4±4.49	76.6±1.50
	F	7	128.1±5.54	134.3±5.61	78.7±2.19
21	M	12	39.0±2.43	149.3±4.40	119.8±3.01
	F	9	44.7±2.83	148.7±4.86	118.7±2.73
30	M	10	18.5±1.70	157.7±6.22	108.0±7.77
	F	12	20.0±1.28	161.9±4.75	108.4±4.97

sponsible for these changes. There is apparently a critical period in the newborn rat during which a series of fundamental enzymatic, metabolic and other hormonal changes occur. During the 21–30 day period after birth, the newborn rat shows significant development of enzymatic drug metabolism and other functions (Halevy, 1979).

These experiments demonstrate that newborn animals are potentially more susceptible to external influences, including anaesthesia, during this critical stage of life. There is a similar period in the human neonate which coincides with the recovery from prenatal hypothyroidism and takes place, in the normal newborn, within the first 48 h after birth.

One may speculate that a hypothyroid neonate may be more vulnerable to anaesthesia, since it may alter thyroid function. Anaesthesia may interfere with thyroid replacement therapy in neonatal hypothyroidism. This is important, since a significant delay in the treatment of the neonates will lead to irreversible brain damage, caused by untreated hypothyroidism. Furthermore, this study highlights the necessity of careful screening for neonatal hypothyroidism.

ACKNOWLEDGEMENTS

This work was supported by the Meadowbrook Medical Education and Research Foundation, Inc., East Meadow, N.Y. The authors gratefully acknowledge the critical review and excellent editorial assistance of Mable Pochedly of Nassau County Medical Center, East Meadow, N.Y.

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ANESTHESIE ET FONCTION DE LA THYROIDE CHEZ LES NOUVEAUX-NES

RESUME

On a étudié sur des rats Wistar nouveaux-nés—âgés de 24 h à 42 jours—la fonction de la thyroide des nouveaux-nés, ainsi que

sa réaction à l'anesthésie à l'héxobarbitone. Des concentrations anesthésiantes d'hexobarbitone marqué au ^{14}C, mélangé à de l'hexobarbitone non marqué ont été injectées dans leur péritoine. Au moment de leur réveil, on a mesuré les concentrations dans le sérum de T3, T3 inversé (rT3) et T4 de même que les concentrations d'héxobarbitone dans le sérum et dans le cerveau entier. On a observé une diminution des concentrations dans le sérum T3 et rT3, de même qu'une augmentation des concentrations dans le T4, après administration d'héxobarbitone à 21 jours et à 30 jours. Cette période semble être critique chez les rats nouveaux-nés On a trouvé une corrélation négative significative entre les changements constatés dans les concentrations de sérum dans les hormones thyroïdiennes et dans les concentrations d'héxobarbitone dans le cerveau entier chez les rats mâles âgés de 30 jours. On pense que des effets similaires peuvent se produire dans le foetus humain ou chez des nouveaux-nés soumis à une anesthésie.

NEONATALE THYROIDFUNKTION UND DIE ANÄSTHESIE

ZUSAMMENFASSUNG

Die Thyroidfunktion im Neugeborenen und ihre Reaktion auf eine Hexobarbitonnarkose wurde an neugeborenen Wistar-Ratten im Alter zwischen 24 Stunden und 42 Tagen Untersucht. Markiertes ^{14}C, gemischt mit unmarkiertem Hexobarbiton wurde intraperitoneal in narkotischen Konzentrationen injiziert. Serum T3, rT3 und T4 sowie Vollhirn-Hexobarbiton-Konzentrationen wurden bei Erwachen gemessen. Ein Abstieg von T3 und rT3 und ein Anstieg von T4-Konzentration wurde 21 und 30 Tage nach Hexobarbiton entdeckt. Das scheint eine kritische Periode bei neugeborenen Ratten zu sein. Eine signifikante negative Verbindung wurde zwischen den Veränderungen in den thyroidalen Hormonkonzentrationen und den Vollhirnkonzentrationen von Hexobarbiton festgestellt, bei 30 Tage alten männlichen Ratten. Man nimmt an, das ähnliche Effekte beim menschlichen Fotus oder Neugeborenen eintreten könnten, der einer solchen Narkose ausgestezt wird.

ANESTESIA Y FUNCION NEONATAL DE LA TIROIDES

SUMARIO

Se estudiaron la función de la glándula tiroides en las ratas Wistar recién nacidas y su respuesta a la anestesia de hexobarbitona, a una edad de entre 24 horas y 42 días. Se inyectaron concentraciones anestésicas de hexobarbitona intraperitoneamente, unas con identificación C^{14} y otras sin identificación y ambas mezcladas. Al despertar se midieron las concentraciones de suero T3, T3 inverso (rT3) y T4 así como las concentraciones de hexobarbitona en el suero y en la totalidad del cerebro. Después de la hexobarbitona se observó una disminución del suero T3 y del rT3, y un incremento en las concentraciones de T4, a los 21 y a los 30 días. Este parece ser un periodo crítico en la rata recién nacida. Así mismo se encontró una correlación negativa de carácter significativo entre los cambios en las concentraciones hormonales del suero de la tiroides y las concentraciones de hexobarbitona en la totalidad del cerebro, en las ratas macho de 30 días. Se sugiere que efectos similares pueden ocurrir en el feto humano o en el recién nacido sujeto a anestesia.

Br. J. Anaesth. (1980), 52, 981

EFFECTS OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS ON THE CARDIAC VAGUS NERVE IN THE GUINEAPIG

S. LEE SON AND D. R. WAUD

SUMMARY

The ability of gallamine, metocurine, pancuronium, tubocurarine and atropine to block the response to postganglionic stimulation of the vagus nerve were measured in isolated, spontaneously beating guineapig atria. From analysis of the results in conjunction with those of earlier assays of concentrations that block effects of preganglionic vagal stimulation, it was concluded that only tubocurarine possessed ganglionic blocking activity. From calculation of the extent of block of muscarinic receptors at drug concentrations which blocked the response to postganglionic vagal stimulation, it was concluded that gallamine and pancuronium have an antivagal action exerted most probably on the postganglionic nerve terminal, and that this action is the most likely explanation of the tachycardia seen clinically with these two drugs.

Gallamine and pancuronium are known to produce tachycardia. In previous studies (Lee Son and Waud, 1978) block of the response to preganglionic vagal stimulation could be demonstrated with pancuronium and gallamine at concentrations which would occur during block of neuromuscular transmission. It has also been shown (Lee Son and Waud, 1977) that, although muscarinic receptors on the atrium can be blocked by neuromuscular blocking agents, the concentrations required are too great to explain the vagal block. The effect of tubocurarine, metocurine, pancuronium and gallamine in blocking stimulation of the postganglionic vagal fibres was examined with a view to assessing the contribution of ganglionic blockade of the vagus nerve to the tachycardia produced by pancuronium and gallamine.

METHODS

Rationale

A drug producing tachycardia could have several sites of action, all involving the vagal innervation of the pacemaker. It could occlude muscarinic receptors on the pacemaker cell, it could interfere with release of acetylcholine from the postganglionic nerve ending, or it could interfere with transmission through the parasympathetic ganglion. The left side of figure 1 summarizes schematically the functional relationship of these sites. There are known examples of all three types of action, including occlusion of muscarinic receptors by atropine and interference with ganglionic transmission by hexamethonium. The presynaptic terminal as a site of drug action has been postulated frequently in connection with action of drugs at the neuromuscular junction (Riker, 1975).

The vagal system might be activated at three points: preganglion, postganglion, or at the muscarinic receptor (fig. 1). Drug influences on the response to presynaptic stimulation and to receptor activation were examined in two previous studies (Lee Son and Waud, 1977, 1978). The present experiments were designed to complement these studies and to use the three set of results to identify the relative contribution of blockade at these three sites of action in the production of tachycardia. Presynaptic stimulation and receptor stimulation were easily obtained. In the former case electric stimulation was applied to the vagal trunk (Lee Son and Waud, 1978). Receptor activation was achieved by administration of the muscarinic agonist carbachol (Lee Son and Waud, 1977). Stimulation of the postganglionic fibres—so crucial to distinguishing ganglionic effects from effects at the terminal nerve ending—is more difficult to do; the postganglionic fibres are embedded in the atrial muscle. Thus any electrical shock applied to these fibres will also be applied to the heart muscle. In the present study the nerve fibres were activated selectively by timing the stimulus pulses so that they occurred during the refractory period of the heart muscle (see below).

The above experimental design can be summarized in terms of how various experimental results would be interpreted. (1) Interference with

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0007-0912/80/100981-07 $01.00

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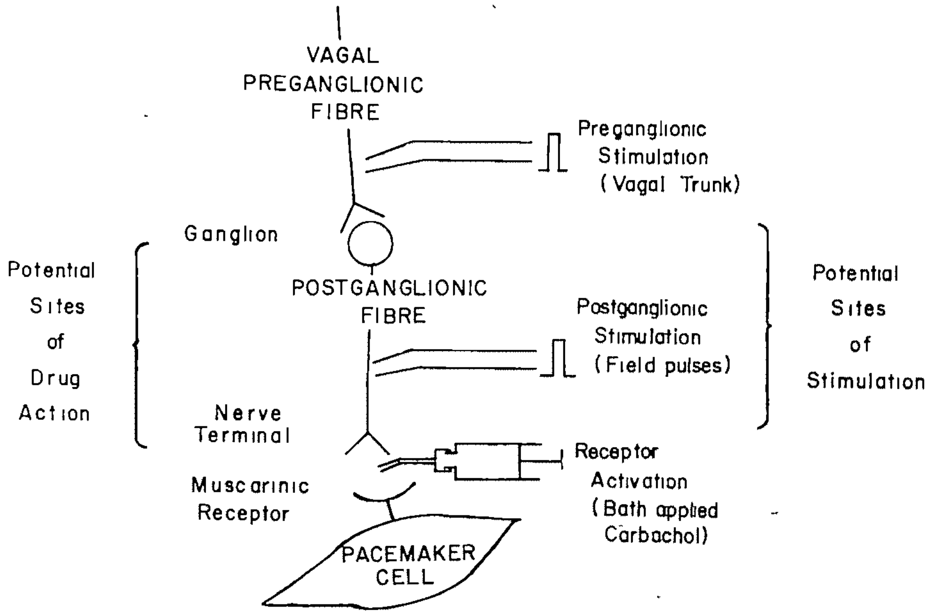
VAGAL PREGANGLIONIC FIBRE
Preganglionic Stimulation (Vagal Trunk)
Ganglion
POSTGANGLIONIC FIBRE
Postganglionic Stimulation (Field pulses)
Nerve Terminal
Receptor Activation (Bath applied Carbachol)
Muscarinic Receptor
PACEMAKER CELL
Potential Sites of Drug Action
Potential Sites of Stimulation

FIG 1. Schematic diagram of vagal innervation of the cardiac pacemaker. A preganglionic fibre passes the signal across the ganglionic synapse to the ganglionic cell, which, through its postganglionic axon, releases acetylcholine to activate a muscarinic receptor on the cardiac pacemaker cell. The left side of the diagram indicates the three sites of drug action of interest in this study. The right side indicates the points at which the signalling system has been activated.

the response to preganglionic stimulation at drug concentrations likely to be present clinically would indicate that a vagal blocking action underlay the tachycardia. (2) Interference with the response to preganglionic stimulation more than that to postganglionic stimulation would indicate a ganglionic blocking action. (3) Interference with the response to carbachol would give a measure of atropine-like activity. (4) Interference with the response to postganglionic stimulation beyond what would be expected from atropine-like activity would indicate an action on the nerve terminal.

The quantitative aspects of applying these principles is described in the discussion.

Experimental

Guineapigs of either sex weighing 250–500 g were killed by a blow on the head and the right atrium was excised rapidly. The vagus nerve was severed near the heart leaving just the vagal fibres within the atrial muscle, including the parasympathetic ganglion cells and the postganglionic nerve fibres. The atrium was suspended in Krebs' solution at 36 °C, which was bubbled with oxygen 95% and carbon dioxide 5%. A pair of external recording electrodes was used to sense surface electrical activity of the spontaneously beating preparation (fig. 2). This signal was used to monitor automaticity by measuring the interval between beats and to trigger a train of impulses used to produce field stimulation. To this end, a pair of stimulating electrodes was placed in the bath, one on either side of the tissue. A voltage applied to these electrodes drove current through both the muscle and nerve cells in the preparation. A pulse generator producing supramaximal pulses of 0.3 ms duration, at a frequency of 100 Hz was used to deliver a train of impulses for field stimulation. This train was timed to come during the refractory period of the atrial muscle cells. Since the refractory period of a nerve is much shorter than that of the cardiac muscle, the nerve will have recovered while the muscle was still refractory. Thus it was possible to stimulate nerve fibres and not the muscle by delivering a train of impulses during this interval. The number of impulses per train was varied from 1 to 9.

Such "field" stimulation produced a transient increase in the interval between beats. This interval increased as the number of impulses per train was increased (fig. 3). Thus a graph relating interval between beats to train length could be

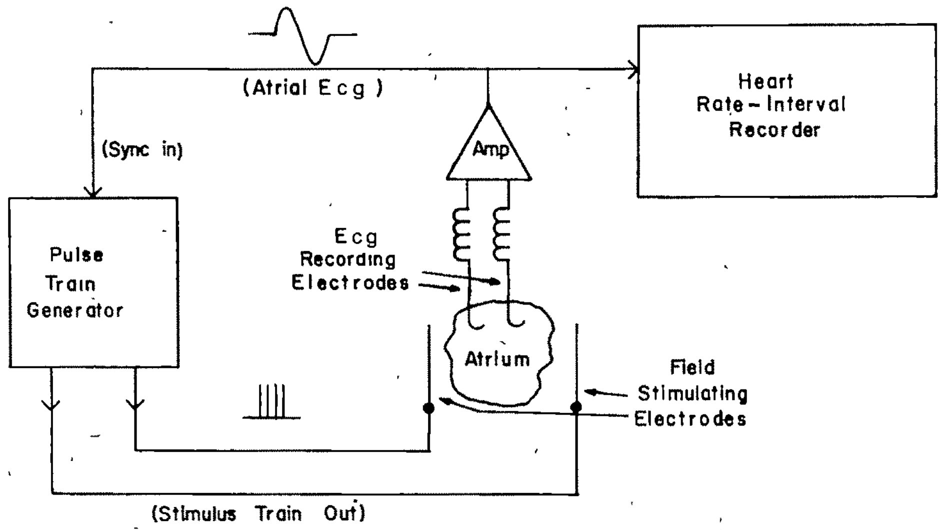

FIG. 2. Schematic diagram of experimental set-up. (In some experiments developed tension was recorded also.)

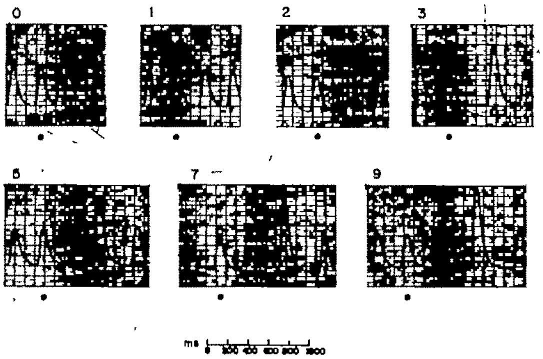

FIG. 3. Examples of the effect of field stimulation on interval between beats. Records of tension exerted by spontaneously beating atria. During the refractory period of the beats labelled by the circles, trains of 0, 1, 2, 3, 5, 7, and 9 pulses were applied to the preparation. The subsequent interval was increased in a graded fashion.

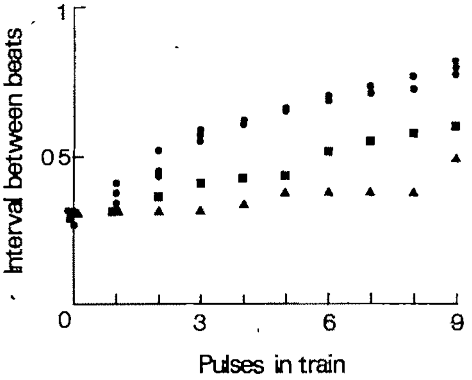

FIG. 4. Example of the effect of pancuronium on the train length–pulse interval relationship. Ordinates: interval between contractions of atrium following train of stimuli (s). Abscissae: number of pulses in stimulus train. Full circles are responses in absence of pancuronium (both before and after washout of the neuromuscular blocking agent). Squares and triangles are values obtained in presence of pancuronium 2×10^{-7} mol litre^{-1} and 5×10^{-7} mol litre^{-1} respectively. The effect of the drugs was to reduce the increase in interval produced by field stimulation.

generated. After the control relationship had been established, a neuromuscular blocking agent or atropine was added to the bath and the response to field stimulation redetermined. Finally, the drug was washed out and a third train length–response curve was obtained to confirm reversibility of drug effect (fig. 4).

The effect of the addition of either one of the neuromuscular blocking agents or atropine was to "scale down" the train length–interval curves; that is, for any given train length, the change in interval between beats was reduced by roughly the same proportional amount. Therefore the fractional depression of the response was averaged over the nine train lengths to yield an objective measure of the effect of each of the drugs. Graded concentrations of the neuromuscular blocking agents and atropine produced graded effects and dose–response curves could be constructed by plotting antagonism to field stimulation against concentration of antagonist (fig. 5). From these curves, ED_{50} values for block of the effect of field stimulation, "FB_{50}" values, were obtained (from an iterative non-linear least squares fitting process which also yielded a value for the standard error of the estimate of FB_{50}. The statistical procedure was analogous to that reported earlier from this laboratory (Waud, 1975)).

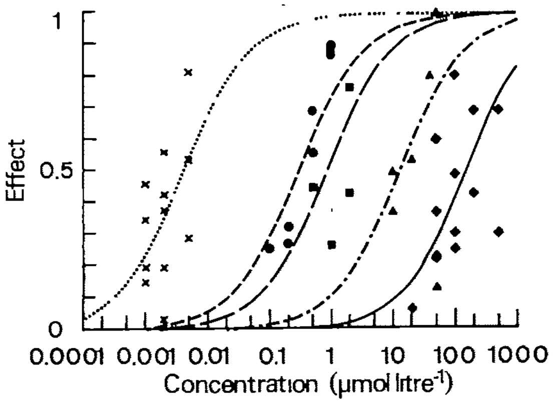

FIG. 5. Summary of concentration–response relationships for the effect of the drugs examined on the response to field stimulation. Ordinates: extents of block of response to field stimulation. Abscissae: drug concentrations. x = atropine; ● = pancuronium; ■ = gallamine; ▲ = metocurine; ◆= tubocurarine. (As a measure of response to the drug the extent of scaling down of curves such as those in figure 4 were used. Specifically, an average over train lengths from 1 to 9 was taken of the function (1 minus control interval at *n* pulses per train minus control interval at 0 pulses per train)/(interval at *n* pulses per train in presence of drug minus interval at 0 pulses per train in presence of drug).) The curves plotted in the figure represent the result of an iterative least squares fit of the function $y = x^P/(x^P + K_i^P)$ to the observed values, where y is response and x the concentration. P governs the common slope and K_i the horizontal location of the i curve respectively. The statistical estimates of K gave the FB_{50} values listed in table I.

RESULTS AND DISCUSSION

Gallamine, metocurine, pancuronium and tubocurarine all depressed the response to field stimulation in a dose-dependent fashion. Figure 4 gives an example of the results obtained and figure 5 summarizes the dose–response relationship for the agents studied. The FB_{50} values obtained are listed in table I. Also included for comparison are "VB_{50}" values, the concentration blocking preganglionic vagal stimulation by 50% (Lee Son and Waud, 1978) and estimates of the apparent dissociation constant, K_B at the cholinergic receptors of the atrial pacemaker (Lee Son and Waud, 1977).

The method of field stimulation developed for this study has proved both powerful and convenient. Sympathetic nerve fibres also lie in the preparation and can be activated by field stimulation (Blinks, 1967). However, we have found that parasympathetic endings can be selectively activated by not stimulating the preparation during every beat, as Blinks did, but by using only a single train of pulses and examining the succeeding interval between beats. Apparently, the response to stimulation of parasympathetic nerve fibres develops more rapidly than that to sympathetic activation. In fact, there seems to be no detectable contribution from the sympathetic system in the present study since propranolol was without effect on the relationship between train length and interval between succeeding beats. Because parasympathetic activation can be selectively achieved by appropriate choice of stimulating parameters and without use of "pharmacological tools," interpretation of the results is not clouded by the possibility of contributions from any drugs in the system other than that being examined.

Absolute drug concentrations have no pharmacological significance. With the neuromuscular blocking agents the concentration effective at the

TABLE I. *Summary of experimental results.* **Lee Son and Waud (1978)*; †*Lee Son and Waud (1977)*, ‡*Fractional receptor occupancy* = $FB_{50}/(FB_{50}+K_B)$

	FB_{50} (µmol litre⁻¹ ±SEM)	VB_{50}* (µmol litre⁻¹ ±SEM)	VB_{50}/FB_{50}	$K_{B(Atrium)}$† (µmol litre⁻¹ ±SEM)	Fraction receptors occluded at FB_{50}‡	Fraction receptors free at FB_{50}
Atropine	0.004±0.001	0.012±0.002	2.90	0.00063±0.00005	0.86	0.14
Tubocurarine	146±44	42.4±9.15	0.29	28.2±3.4	0.84	0.16
Metocurine	12.6±5.37	17.6±3.27	1.4	7.5±0.93	0.63	0.37
Pancuronium	0.292±0.115	0.532±0.104	1.88	0.13±0.008	0.69	0.31
Gallamine	0.833±0.372	2.86±0.573	3.57	1.1±0.05	0.43	0.57
Hexamethonium	>100	60	<1			

neuromuscular junction should be considered. Since roughly 90% of the end-plate receptors must be occluded to produce a full neuromuscular block, we may take the concentration producing this effect as relevant to the clinical concentration. The dissociation constants at the neuromuscular junction are tubocurarine 0.107 µmol litre^{-1} ± 0.005 (SEM); dimethyltubocurarine 0.0552 µmol litre^{-1} ± 0.0093 (SEM); pancuronium 0.0247 µmol litre^{-1} ± 0.0014 (SEM); gallamine 0.458 µmol litre^{-1} ± 0.031 (SEM) respectively (Lee Son and Waud, 1977). Thus clinical neuromuscular block would involve concentrations of about 0.96 µmol litre^{-1} for tubocurarine, 0.50 µmol litre^{-1} for dimethyltubocurarine, 0.22 µmol litre^{-1} for pancuronium and 4.12 µmol litre^{-1} for gallamine. Thus, for example when we see in figure 5 and table I that it requires roughly 150 µmol litre^{-1} of tubocurarine to block field stimulation, we can conclude the drug would produce no block at this anatomical level when given clinically.

The measure of field stimulation used, FB_{50}, is an arbitrarily chosen endpoint. Similarly, VB_{50} values previously obtained also involve no absolute standard. Thus a frame of reference is needed for comparison of drug effects on pre- and postganglionic stimulation. Atropine provides such a measure. The site of block with atropine is common to the pathway of signal transmission for both pre- and postganglionic vagal stimulation. Therefore, the ratio of VB_{50}/FB_{50} for atropine represents the value expected from a drug which exerts no differential effect on pre- *v.* postganglionic stimulation, that is a drug not acting at ganglia. Table I shows that this ratio is 2.9 for atropine. For comparison, figure 6 shows the effect of hexamethonium on the system. VB_{50} was about 60 µmol litre^{-1}, whereas hexamethonium 100 µmol litre^{-1} produced negligible block of field stimulation, that is the FB_{50} was considerably greater than 100 µmol litre^{-1}. Thus the ratio VB_{50}/FB_{50} would be much less than unity. The neuromuscular blocking agents can now be examined against this background. The values of 3.57, 1.88 and 1.44 seen with gallamine, pancuronium and metocurine respectively were of the same order of magnitude as that seen with atropine. On the other hand, tubocurarine blocked responses to preganglionic stimulation more selectively than did atropine. The value of VB_{50}/FB_{50} was 0.29, less than unity as seen also with hexamethonium and reflecting the well known ganglionic blocking activity of tubocurarine (Hughes and Chapple, 1976).

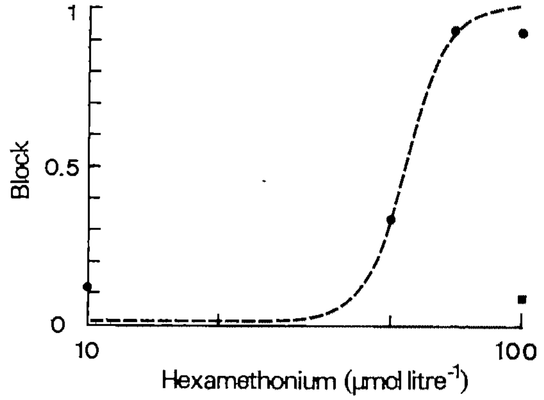

FIG. 6. Effect of hexamethonium. Circles and broken line give concentration–response relationship for block of preganglionic stimulation measured as described previously (Lee Son and Waud, 1978). Square shows absence of effect of hexamethonium on response to field stimulation.

The absence of a vagal ganglionic blocking action of gallamine and pancuronium means one must look peripheral to the ganglion to find the site of the vagal blocking action of these agents observed previously (Lee Son and Waud, 1978). Atropine again provides the clue. From the atropine–muscarinic receptor dissociation constant, K_B, of 0.00063 µmol litre^{-1} (Lee Son and Waud, 1977) one can calculate that the receptor occlusion by atropine at the FB_{50} of 0.004 µmol litre^{-1} would be (Waud, 1968):

$$Y = [B]/([B]+K_B)$$

(where Y is a fraction of receptors occupied by the antagonist B and $[B]$ is the concentration of the antagonist)

$$= 0.004/(0.004+0.00063) = 0.86$$

Corresponding values can be calculated for the neuromuscular blocking agents examined and are given in table I, with the fraction of receptors that would still be available to the transmitter. Tubocurarine gives values indistinguishable from those for atropine, indicating that this neuromuscular blocking agent has no effect on the response to field stimulation beyond that which would be expected from its (weak) ability to block muscarinic receptors. On the other hand, gallamine, pancuronium and metocurine leave roughly three to five times as many receptors free when they are at their FB_{50} concentrations. This means they are blocking field stimulation by some mechanism beyond a simple atropine-like receptor occlusion. The site of this effect must be peripheral to the ganglionic synapse and proximal to the muscarinic receptor. The postganglionic axon and the nerve terminal thereof are two potential sites of action in this interval. The latter, the nerve ending, seems a more likely candidate since appreciable local anaesthetic activity has not been found with competitive neuromuscular blocking agents (Jarcho et al., 1950; Riker and Wescoe, 1951; Buckett et al., 1968). The nerve terminal action is not clinically significant in the case of metocurine since it occurs at concentrations too great to be likely to occur clinically. However, this presynaptic action appears to be the best candidate to explain the tachycardia seen with gallamine and pancuronium.

A presynaptic site of action of drugs is not without ample precedent (Langer, 1974; Riker, 1975). Of particular interest is the adrenergic terminal where analogues of noradrenaline depress transmitter output (Berthelsen and Pettinger, 1977). In this context, it is not surprising that quaternary nitrogen compounds might similarly interfere with release at a cholinergic nerve ending. It has also been suggested that clonidine, which acts at the presynaptic alpha-adrenergic receptor, might also act on a presynaptic receptor to inhibit release of transmitter from cholinergic fibres (Werner, Starke and Schumann, 1972). However, the relationship of this phenomenon to the presynaptic action seen in the present study is not clear. At present the experiments only reveal that the presynaptic effect exists, and do not shed light on its mechanism.

ACKNOWLEDGEMENT

The authors are grateful to Dr B. E. Waud for helpful discussion and criticism during preparation of this manuscript.

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EFFETS DES AGENTS DE BLOCAGE NEUROMUSCULAIRE NON DEPOLARISANTS SUR LE NERF PNEUMOGASTRIQUE CARDIAQUE DU COCHON D'INDE

RESUME

On a mesuré sur des oreillettes de cochons d'Inde, isolées et battant spontanément, la faculté que possèdent la gallamine, la métocurine, le pancuronium, la tubocurarine et l'atropine de bloquer la réaction du nerf pneumogastrique à la stimulation postganglionnaire. De l'analyse des résultats obtenus, conjointement avec les analyses effectuées antérieurement sur les concentrations qui bloquent les effets des stimulations pneumogastriques préganglionnaires, on a conclu que seule la tubocurarine possède des propriétés de blocage ganglionnaire. D'après les calculs effectués sur l'importance du blocage des récepteurs muscariniques aux concentrations de médicament qui bloquent la réaction à la stimulation pneumogastrique postganglionnaire, on a conclu que la gallamine et le pancuronium ont une action antipneumogastrique très probablement exercée sur le point terminal postganglionnaire du nerf et que cette action est l'explication la plus vraisemblable de la tachycardie que l'on constate cliniquement avec ces deux médicaments.

WIRKUNGEN EINES NICHT-POLARISIERENDEN NEUROMUSKULÄREN BLOCKIERUNGSMITTELS AUF DEN VAGUSNERV BEIM MEERSCHWEINCHEN

ZUSAMMENFASSUNG

Die Fähigkeit von Gallamin, Metocurin, Pancuronium, Tubocurarin und Atropin, die Reaktion des Vagusnervs auf retroganglionare Stimulierung zu blockieren, wurde in isolierten, spontan schlagenden Atrien von Meerschweinchen gemessen. Aus der Resultatanalyse zusammen mit den Resultaten früherer Prüfungen von Konzentrationen, die präganglionare Vagusstimulation blockieren, wurde geschlossen, dass dass nur Tubocurarin uber eine solche ganglionare Blockierungsaktivität verfugt. Aus dem Blockierungsausmass bei Muscarinrezeptoren nach Drogenkonzentrationen, die die Vagusstimulation blockierten, wurde festgestellt, dass Gallamin und Pancuronium eine Antivagus-Wirkung haben, die wahrscheinlich auf das retroganglionäre Nervende wirkt, und dass diese Wirkung die wahrscheinlichste Erklarung fur die klinisch bei diesen beiden Drogen beobachtete Tachykardie ist.

EFECTOS DE LOS AGENTES DE BLOQUEO NEUROMUSCULAR Y NO DESPOLARIZANTES SOBRE EL NERVIO VAGO CARDIACO EN CONEJOS

Se midió, en aurículas de conejos aisladas y latiendo espontáneamente, la habilidad de la gallamina, la metocurina, el pancuronium, la tubocurarina y la atropina, para bloquear la respuesta a la estimulación posgangliónica del nervio vago. Mediante el análisis de los resultados y en coordinación con los anteriormente establecidos correspondientes a las concentraciones que bloquean los efectos de la estimulación vagal pregangliónica, se concluyó que sólo la tubocurarina posee actividad ganglionica de bloqueo. A partir de los calculos del grado de bloqueo de los receptores muscarinicos, para concentraciones de drogas que bloquearon la respuesta de la estimulación vagal posganglionica, se concluyó que la gallamina y el pancuronium poseen una acción antivagal que se ejerce, casi con seguridad, en el terminal del nervio post-ganglionico, de forma que esta actividad es la explicación más probable de la taquicardía que se vé a nivel clínico con estas dos drogas.

Br. J. Anaesth. (1980), 52, 989

ISOBUTENE FORMATION DURING HALOTHANE ANAESTHESIA IN MAN

V. HEMPEL, R. MAY, H. FRANK, H. REMMER AND U. KÖSTER

SUMMARY

The concentrations of volatile hydrocarbons were studied in breath samples from patients before and after anaesthesia. In patients to whom halothane was administered, there was a significant increase in the concentration of isobutene (from 0.43 ± 0.09 to 4.66 ± 2.22 nmol litre^{-1}). There was no change in the concentration of isobutene in six patients anaesthetized with ketamine and diazepam. The concentrations of ethane and pentane were not altered significantly in either group.

Lipid peroxidation is thought to play a role in halothane-induced liver injury (Brown, 1972; Reynolds and Moslen, 1974; Plaa and Witschi, 1976). However, the investigation of lipid peroxidation had been confined to the examination of tissue samples, until Riely, Cohen and Liebermann (1974) discovered that this reaction could be monitored during *in vivo* experiments by the measurement of ethane concentrations in expired air. In such studies ethane or pentane have been determined to be the more abundant volatile hydrocarbons resulting from lipid peroxidation (Horvat et al., 1964; Dillard, Dumelin and Tappel, 1977; Dumelin and Tappel, 1977; Hempel and Köster, 1978). Using an improved gas chromatographic method (Frank, Hintze and Remmer, 1980) we are able to determine concurrently both hydrocarbons and other C1–C5 hydrocarbons in human breath. The aim of this study was to identify and to quantify the volatile products of lipid peroxidation in the breath of patients who had undergone clinical anaesthesia with halothane and of control patients anaesthetized without halogenated anaesthetics.

PATIENTS AND METHODS

Patients were women (age range 38–56 yr) undergoing abdominal hysterectomy under general anaesthesia. Informed consent to the study was obtained the day before operation. Breath samples were taken before and after the operation (as soon as the patients were able to exhale) into an aluminium-lined plastic bag ("Plastigas", Linde, München). A third sample was taken 2 h later in the recovery room.

Two hundred millilitre of the breath samples was aspirated on a steel column (505 × 0.3 cm) packed with Porasil C (Linde-AG, München) which was cooled to 140 K in a mixture of liquid nitrogen and ethanol. The column was fitted to a gas chromatograph (Hewlett–Packard 5720 A) via a six-port valve. For desorption of the volatile hydrocarbons, the column was immersed in a water bath at 90 °C.

Chromatography was performed on a steel column (5 m × 3 mm) packed with Porasil C using nitrogen as carrier gas (30 ml min^{-1}). Oven temperature was 60 °C. The hydrocarbons were detected by a flame-ionization detector (hydrogen 40 ml min^{-1}, air 220 ml min^{-1}) and the peak areas calculated with an integrator (Hewlett–Packard 3380 A) which plotted the chromatograms (fig. 1). The peaks were identified by comparison of the retention times with those of samples of the pure hydrocarbons and, in the case of isobutene, by mass spectrometry also. Molar response factors were calculated from chromatography of a standard mixture of hydrocarbons (about 1 p.p.m. each) in nitrogen (Linde AG, München). The retention times were (min): ethane 2.9, ethylene 3.5, propane 4.0, propene 6.6, iso-pentane 11.5, pentane 12.2, 1-butene 13.5, trans-butene 19.2, iso-butene 20.5, cis-butene 23.5 and halothane 26.4.

Seventeen patients were investigated. Eleven received halothane and six were anaesthetized without halothane.

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0007-0912/80/100989-04 $01.00

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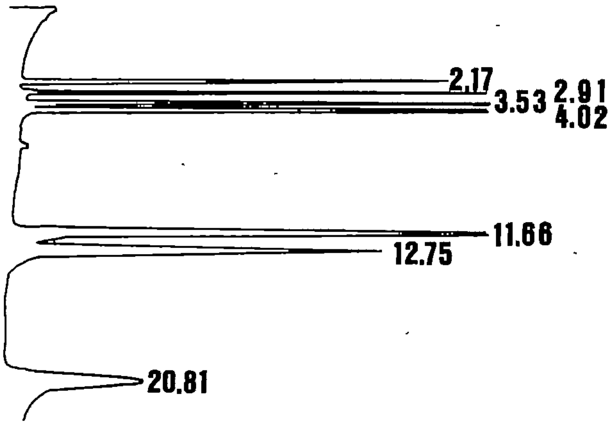

FIG 1. Representative gas chromatographic tracing. The main peaks are ethane (2.91), ethylene (3.53), propane (4.02), iso-pentane (11.66), pentane (12.75) and iso-butene (20.81). A minor shift of retention times result from different handling of the water bath for desorption of hydrocarbons from the sample columns.

Anaesthesia was induced with etomidate 0.3 mg kg^{-1}. Suxamethonium was administered, the trachea intubated and the lungs ventilated with halothane 1.0–1.5% in pure oxygen (purity 99.99%, Messer–Griesheim, Darmstadt). This gas mixture was found to be free of the hydrocarbons under investigation. Nitrous oxide and oxygen from the central gas supply of our hospital had to be avoided on account of the content of hydrocarbons. If anaesthesia was inadequate a small dose of fentanyl was added. During the operation neuromuscular blockade was achieved with pancuronium.

In the control group, which did not receive halothane, anaesthesia was maintained with repeated doses of ketamine and diazepam.

RESULTS

The concentrations of ethane, propane, pentane, iso-pentane and iso-butane obtained in both test and control groups are presented in table I. The concentrations of ethylene, propene, butane, 1-butene, cis- and trans-butene could not be given in nmol $litre^{-1}$, since our standard mixture did not contain these hydrocarbons.

There was a significant increase in the concentration of iso-butene following the administration of halothane. Ethane and propane concentrations showed no change during anaesthesia. The other substances mentioned above were present in trace concentrations.

DISCUSSION

Halothane is known to induce lipid peroxidation in laboratory animals (Brown, 1972; Reynolds and Moslen, 1974; Hempel and Köster, 1978). Ethane and pentane have been shown to be reliable indicators of this reaction (Dillard, Dumelin and Tappel, 1977; Riely, Cohen and Liebermann, 1974). However, in man exhalation of these hydrocarbons is not increased following halothane anaesthesia, as our results demonstrate.

The small increase in the pentane concentrations in both groups may be a result of the ventilation with pure oxygen, since high partial pressures of oxygen may cause lipid peroxidation (Plaa and Witschi, 1976). The most important

TABLE I. *Content of hydrocarbons in breath samples before (I), immediately after (II) and 2 h after (III) anaesthesia in patients anaesthetized with halothane* (n = *11*) *and with ketamine and diazepam* (n = *6*) (*nmol* $litre^{-1}$ ± *SD*). **Significant difference from the value before anaesthesia* (P < *0.01, Student's* t *test*)

	Halothane			Controls		
	I	II	III	I	II	III
Ethane	0.22 ±0.07	0.26 ±0.17	0.19 ±0.06	0.36 ±0.09	0.32 ±0.08	0.36 ±0.06
Propane	0.20 ±0.06	0.13 ±0.06	0.10 ±0.06	0.31 ±0.09	0.25 ±0.10	0.33 ±0.11
Pentane	0.47 ±0.32	1.31 ±0.82	0.66 ±0.31	0.64 ±0.21	0.96 ±0.71	0.94 ±0.37
Iso-pentane	0.38 ±0.11	0.50 ±0.21	0.38 ±0.14	0.61 ±0.36	0.48 ±0.16	0.57 ±0.13
Iso-butene	0.43 ±0.09	4.66* ±2.22	2.88 ±1.04	0.36 ±0.14	0.31 ±0.11	0.34 ±0.21

finding of this investigation is the increase in the isobutene concentration in the exhaled air during halothane anaesthesia. Anaesthesia in the control group, administered under exactly the same circumstances and with the same anaesthetic circuits and apparatus, did not lead to an increase in isobutene concentration. Thus, it can be ruled out that isobutene is an artefact arising from plastic or rubber equipment. Since no isobutene was found in the halothane (Fluothane, I.C.I.) isobutene must be an endogenous product.

As a possible source of isobutene, one can consider the degradation of terpenes. The membranes of the endoplasmic reticulum, where the biotransformation of halothane occurs, contain lipids with a terpene structure called "dolichols" (Behrens and Leloir, 1970). The dolichols act as cofactors of glycogen synthesis, which is impaired by halothane (Rosenberg, Haugaard and Haugaard, 1977). It is possible that the degradation of dolichols by lipid peroxidation is the cause of this impairment of glycogen synthesis. Isobutene may occur at some stage during the synthesis of steroids from squalene or one of the precursors. Another possible source of isobutene are the ubiquinones. These function as hydrogen carriers in the mitochondria and if the isobutene arises from the biodegradation of the ubiquinones, it is more likely that the further metabolism of isobutene is prevented by halothane than that the degradation is enhanced. Metabolism of halothane takes place in the endoplasmic reticulum, and it is difficult to imagine that reactive intermediates of halothane metabolism can reach the mitochondria where the ubiquinones are located. Recently, an animal model of hepatic necrosis caused by halothane has been demonstrated (Ross, Daggy and Cardell, 1979; McLain, Sipes and Brown, 1979), the molecular mechanism of which is covalent binding of halothane metabolites to macromolecules. Mansuy, Nastainczyk and Ullrich (1974) demonstrated that a biradical can act as the reactive intermediate in covalent binding during halothane metabolism. The mechanisms of covalent binding and lipid peroxidation are not mutually exclusive. Radical scavengers may prevent both reactions. As Brown, Sipes and Sagalyn (1974) have demonstrated, halothane does not decrease glutathione concentrations as do other agents causing lipid peroxidation. Apart from glutathione, other radical scavengers can play a role in protecting susceptible structures against lipid peroxidation. Radical scavengers may exist which have a terpene-like structure and undergo lipid peroxidation when attacked by radicals and this could mean that isobutene is a very sensitive indicator of lipid peroxidation in man.

It is known that hydrocarbons are metabolized to the corresponding alcohols by the drug-metabolizing system cytochrome P-450, as shown by *in vitro* experiments. Recently it has been demonstrated (Frank, Hintze and Remmer, 1980), that inhibition of the drug-metabolizing system *in vivo* leads also to an increase in exhaled hydrocarbons. However, this is not a sign of lipid peroxidation if the increase is small. It is well known that halothane is an inhibitor of the drug metabolizing system (Brown, 1971; White, Johnston and Pudwill, 1975). Consequently, the increase in the concentration of isobutene may result from a decrease in the metabolism of this endogenous hydrocarbon. However, the origin of the endogenous isobutene remains obscure and further animal experiments are necessary to clarify its cause.

In conclusion, the volatile hydrocarbons present in the breath of patients, which can serve as indicators of lipid peroxidation, have been identified and quantified for the first time. Whether halothane, in the concentrations used for anaesthesia, induces lipid peroxidation in man remains uncertain.

ACKNOWLEDGEMENTS

We are indebted to Ms M. Kommerell for experienced technical assistance.

This work was supported by Grant No He 914/1 from the Deutsche Forschungsgemeinschaft.

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FORMATION D'ISOBUTENE AU COURS D'UNE ANESTHESIE A L'HALOTHANE CHEZ L'HOMME

RESUME

On a étudié sur des échantillons de respiration émanant de patients et prélevés avant et après leur anesthésie, les concentrations d'hydrocarbures volatils. Parmi les patients auxquels on avait administré de l'halothane, on a constaté une augmentation significative de la concentration d'isobutène (celle-ci passant de 0,43 ± 0,09 à 4,66 ± 2,22 nmol litre^{-1}). Il n'y a eu aucun changement dans la concentration d'isobutène des six patients qui avaient été anesthésiés à l'aide de kétamine et de diazépam. Les concentrations d'éthane et de pentane n'ont été significativement modifiées ni dans un groupe, ni dans l'autre.

ISOBUTANBILDUNG WÄHREND HALOTHANNARKOSE BEIM MENSCHEN

ZUSAMMENFASSUNG

Die Konzentrationen fluchtiger Kohlenwasserstoffe wurden anhand von Atemproben von Patienten vor und nach der Narkose studiert. Bei Halothanpatienten kam es zu einem wesentlichen Anstieg der Isobutankonzentration (von 0,43 ± 0,09 auf 4,66 ± 2,22 nmol Liter^{-1}). Bei sechs mit Ketamin und Diazepam narkotisierten Patienten kam es zu keinen Anderungen der Isobutankonzentrationen. Die Athan- und Pentankonzentrationen waren im keiner der Gruppen wesentlich verändert.

FORMACION DE ISOBUTENO EN EL HOMBRE DURANTE LA ANESTESIA CON HALOTANO

SUMARIO

Se estudiaron las concentraciones de hidrocarburos volátiles en muestras de la respiración de pacientes, antes y después de la anestesia. En aquellos pacientes a los que se administró halotano, hubo un incremento significativo en la concentración de isobuteno, de 0,43 ± 0,09 a 4,66 ± 2,22 nmol litre^{-1}). No se apreció cambio alguno en la concentración de isobuteno en seis pacientes anestesiados con ketamina y diazepam. Las concentraciones de etano y de pentano no cambiaron de manera significativa en ningun grupo.

Br. J. Anaesth. (1980), 52, 993

ANAESTHETIC MANAGEMENT OF TRACHEAL SURGERY USING THE NEODYMIUM–YTTRIUM–ALUMINIUM–GARNET LASER

G. VOURC'H, M. L. TANNIERES, L. TOTY AND C. PERSONNE

SUMMARY

A new technique for the management of tracheal or bronchial lesions (tumours or stenosis) using the NdYAG laser and bronchoscopy, was used in 55 patients without complications The anaesthetic problems are discussed. In some circumstances the procedure may be performed using sedation and topical anaesthesia. In most, general anaesthesia was used, controlled ventilation being achieved through the bronchoscope using a modification of the Sander's injector with a mixture of 50% nitrogen and oxygen to avoid the risk of fire.

Microlaryngeal surgery using a carbon dioxide laser is now a well established procedure. The anaesthetic problems involved have been described by various authors (Strong and Jako, 1972; Birch, 1973; Andrews and Moss, 1974; Konchigeri and Shaker, 1974; Snow et al., 1974; Strong, 1975; Shaker et al., 1976; Strong et al., 1976; Vourc'h, Tannières and Frèche, 1979). The advantages of the laser are the absence of bleeding and oedema, and rapid healing. One of the risks is the ignition of unprotected rubber or plastic tubes, and of anaesthetic gases, as a result of the intense heat generated by the laser beam (Snow et al., 1976; Vourc'h and Tannières, 1979).

The introduction of the carbon dioxide laser technique to the trachea and bronchial tree creates new problems since the beam travels, like light, in a straight line and cannot therefore reach lesions situated deep within the air passages. Only one report (Laforest, Berger and Vaughan, 1976) has been published describing relief of tracheal obstruction using the carbon dioxide laser. However, the neodymium–yttrium–aluminium–garnet laser (NdYAG) overcomes this difficulty since the beam is carried through a flexible fibre and can be aimed in any direction under bronchoscopic control.

This report describes the apparatus used, the anaesthetic technique adapted for this new device, and our preliminary clinical results in 55 patients.

APPARATUS

The principle of the NdYAG laser has been described by Snow (1977). The apparatus used in this study (Compagnie Industrielle des Lasers (CILAS), Route de Nozat, 91460 Marcoussis, France) provides an output of up to 90 W in the infra-red wave length ($\lambda = 1.06$ mμ). A combined pilot beam (helium and neon) produces a bright red spot which can be aimed towards the lesion. The two beams are conveyed through the same flexible fibre, of 1 mm diameter. The core is made of silica enclosed in a silicone sheath. A coaxial Teflon tube (1.8 mm external diameter) allows the injection of compressed air (3 litre min^{-1}) to cool the tip of the laser fibre, prevent condensation on the endoscope and to disperse fumes.

Since the laser beam has a 10° divergence, the diameter of the site of impact varies with the distance between the tip of the fibre and the target. In practice that distance is maintained between 5 and 10 mm.

The laser fibre is inserted through the biopsy channel of a standard rigid bronchoscope or may be used with a T3 Olympus flexible bronchoscope fitted with a 2.7 channel. In either case, the laser fibre can be bent in any direction and aimed towards the lesion. The power, time and distance from the lesion can be adjusted according to the needs of the patient. *Coagulation*: 30 W for 0.7–1 s over a surface of about 3 mm, at a distance of 10 mm. *Excision*: 40–70 W for 0.3 s in bursts of one every 2 s, at a distance of about 5 mm.

Each burst triggers an auditory signal and a counter records the number of bursts. A foot

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0007–0912/80/100993–05 $01.00

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switch controls first the jet of compressed air and then the laser itself.

Since the laser beam can induce severe burns, particularly to the eyes (Leibowitz and Peaçock, 1969), special goggles (provided by CILAS) must be worn for protection by the attending personnel. They provide a reduction of 10^6 at a wavelength of 1.06 mμ.

The energy delivered by the NdYAG laser is absorbed better by tissue containing melanin or haemoglobin. It may, therefore, be necessary to apply a dye such as methylene blue to a white surface before using the laser.

METHODS

In the presence of heat, nitrous oxide and oxygen support and invigorate combustion. Thus ventilation should be with air or with a 50% mixture of oxygen in nitrogen, which has been found to be safe.

The problems of achieving both ventilation and anaesthesia for endoscopic bronchial surgery with the laser are not easy to overcome and we describe and discuss our method under various headings.

Patients

All had lesions within the bronchial tree: tumours, benign or malignant (papillomas, granulomas, carcinoids, cancers), or scar tissue following prolonged intubation or tracheotomy. Some patients had a degree of respiratory obstruction or of respiratory insufficiency and could not tolerate further respiratory depression. Most had inflammation of the mucosa and topical analgesia is ineffective. Although the procedure is painless, it was essential to avoid coughing or restlessness to ensure accurate aim of the beam.

Anaesthesia

Premedication always included atropine or hyoscine and sedation was used if appropriate to the patient's condition. Anaesthesia was conducted as follows.

Co-operative patients with normal respiratory function. The procedure could have been performed using topical analgesia and sedation such as neuroleptanalgesia, using dehydrobenzperidol (or a sedative drug such as diazepam) and phenoperidine or fentanyl. Any residual respiratory depression caused by the analgesic was antagonized with naloxone.

Patients requiring general anaesthesia. Various examples had to be considered:

In adults, if a fibrescope was available, the procedure could be carried out using a large cuffed endotracheal tube, following the standard techniques described by Tahir (1972) and MacNaughton (1975). In Tahir's method, the fibrescope is inserted through a rubber diaphragm within the endotracheal tube and ventilation of the lungs is achieved either manually or mechanically, using enriched air and halothane. If MacNaughton's technique is adopted, ventilation is with enriched air only.

In other cases (in children or when a rigid bronchoscope was used) lung inflation using the Sander's injector was found satisfactory but the apparatus had to be modified. The standard injector fitted at the proximal (machine) end of the bronchoscope was found to be unsatisfactory because the bulk of the eyepiece and the leaks through the side vents of the bronchoscope resulted in inadequate ventilation. This was particularly so when the lesion was just below the cords or when the bronchoscope was introduced through a tracheostomy. A 16-gauge brass tube was therefore welded to the inside of the bronchoscope, opening at the tip. This was found to be entirely satisfactory in all patients. Since air or enriched air was used for ventilation, unconsciousness was achieved during prolonged procedures by an i.v. infusion of short-acting agents such as Althesin, methohexitone or propanidid.

In practice, the following technique was used. An i.v. infusion was established. A dose of thiopentone sufficient to obtund the eyelash reflex was administered, followed by suxamethonium. The lungs were ventilated with oxygen and the bronchoscope inserted. Ventilation was then performed by manual control of the injector and muscle relaxation was achieved using a suxamethonium infusion. When the procedure was completed and the bronchoscope removed the lungs were ventilated using a mask or through the tracheostomy until recovery was complete.

The jet of compressed air occasionally sprayed blood down into the bronchial tree and it obscured the view through the bronchoscope. It was then necessary to stop ventilation for a few seconds to provide the operator with a clear field of vision and apply suction.

CLINICAL RESULTS

During a 10-month period, 55 patients were treated without accident or complication (table I). This corresponds to 110 operations since most patients required treatment on more than one occasion. Twenty-three patients were treated at a single session, the others between two and five. It is too early to draw conclusions from such a small series but the technique is promising.

TABLE I. *Lesions treated in 55 patients*

Cancers (28)	Untreated tracheal cancers	12
	Recurrent tracheal cancers	13
	Miscellaneous	3
Benign tumours (4)	Amyloid tumour	1
	Solitary papillomas	2
	Diffuse papillomas	1
Moderately malignant tumours (4)	Carcinoids	3
	Cylindroma	1
Iatrogenic stenosis (15)	Palliative procedure	8
	Radical procedure	7
Granulomas (4)		4
Total		55

Tracheal or bronchial carcinoma (28 patients)

Two groups of patients have been treated.

Tracheal carcinomas recently detected, in acute respiratory distress (12 patients). In nine, one single session achieved immediate relief. In three, the resection was more difficult because of bleeding. In the most advanced tumours, tracheal intubation for 24 h to 3 days allowed time for radiotherapy. These 12 cases were technically successful.

Recurrent carcinoma already treated medically or surgically. Seven followed surgical procedures (five pneumonectomy, two bilobectomy, and resection–anastomosis). The growth was situated either on the suture line or on the lowest tracheal rings and was obstructing either the trachea itself or the main bronchus. All patients had received radiotherapy before or after surgery and were unsuitable for any other therapy. Clearly the use of the laser was purely palliative and might be repeatable.

Six other lesions were not operable and had been irradiated. The laser was the only means of providing temporary relief as the trachea or main bronchus had been invaded.

In two patients, oesophageal carcinoma had invaded the pars membrana of the trachea and in one patient a thyroid tumour had invaded and obstructed the trachea. Treatment with the laser, followed by radiotherapy, afforded relief lasting 7 months.

Benign tumours (four patients)

These are very rare.

An amyloid tumour, 8 mm diameter, involved the middle part of the trachea obstructing a third of the lumen. It was resected in one session. Diathermy might have achieved the same result, but the laser treatment was completely successful. A papilloma of the main bronchus, situated on the pars membrana was destroyed following five bursts with 70 W.

A laryngo–tracheal papilloma had developed for 10 years. The patient underwent tracheotomy and was completely relieved; the tracheostomy was then closed. A papilloma of the left main bronchus in a respiratory cripple who was unfit for major surgery was treated.

Moderately malignant tumours (four patients)

A carcinoid tumour of the left lower lobe bronchus required three treatment sessions for resection although bronchoscopy had shown the pedicle to be thin. It is still too early to tell whether the resection was complete.

Another carcinoid tumour of the apical segment of the right lower lobe bronchus was obstructing the main bronchus, moving up and down on its stalk. It was resected in one session, another session being required to treat the pedicle. This was the only therapy feasible for this patient who had very severe respiratory disease ($FEV_1 = 840$ ml).

The third carcinoid tumour was in a 72-yr-old patient and again the laser offered the only possible treatment. It was a recurrent growth. The patient had been submitted to a carinal resection (Barclay's procedure) 13 years previously. The new carina was invaded by a tumour obstructing the whole lumen of the left main bronchus, while the right was partially occluded. The left main bronchus was nearly completely cleared of tumour in three sessions.

The fourth patient had a widespread recurrent cylindroma as a sequel to left pneumonectomy performed 12 years before, followed by radiotherapy. A year previously an oesophago-coloplasty had been performed to treat oesophageal stenosis caused by recurrence of the cylindroma and by radiotherapy. Two-thirds of the right main bronchus was obstructed. Otherwise the patient's condition was good. Following two laser sessions the right main bronchus was cleared, but recurrence is obviously likely.

Iatrogenic tracheal stenosis following either tracheotomy or intubation (15 *patients*)

These vary considerably in their site, from the subglottic region to the lower third of the trachea; the speed of their development, from a few weeks to some years; their length—simple diaphragm or a long cylinder, and their severity. They often affect young otherwise healthy patients.

It is obvious that the laser beam cannot attack more than the fibrous tissue implanted on the tracheal wall. Seen through the bronchoscope, the impression is of a funnel-like lesion arising from an endotracheal stenosis. The main part of the stenosis is always a result of collapse of the tracheal wall itself. In some cases it may stem from the destruction of the cartilage rings.

Our preliminary trials with the laser have fully endorsed these findings. Any tracheal stenosis was primarily because of collapse of the tracheal wall and the fibrous tissue growing into the lumen merely increased the restriction of the hour-glass-like collapse of the cartilage framework.

It was interesting to note that in nearly all examples of narrow stenosis (less than 5 mm), the laser produced a 70–100% increase in the lumen size, which afforded immediate relief to patients in respiratory distress. This did not achieve radical cure, however, because the obstruction of the tracheal wall persisted. A subsequent resection–anastomosis had to be performed, but in excellent respiratory conditions and not as an emergency procedure.

In eight patients, laser therapy was preparatory to a resection–anastomosis. However, in seven cases of obstruction because of a diaphragm it has apparently achieved radical cure, thus avoiding a surgical procedure; three of these patients could not have tolerated major surgery.

Granulomas (four patients)

Laser therapy is the ideal technique for the cure of granulomas developing on a tracheal or bronchial suture or following prolonged tracheal intubation in intensive care units. They must not be neglected since they may lead to a fibrous stenosis.

SPECIAL PROBLEMS

Haemorrhage. Bleeding occurs mainly from malignant tumours. The laser does not obviate it completely, but it is less troublesome than with diathermy or piecemeal surgical removal. It may be disturbing even though limited to a few drops, but is easily aspirated. However, the jet of air triggered by the laser, and particularly the blast of gases coming from the Sander's injector, sprays the blood down into the trachea and may obscure the view. This difficulty can be avoided by withdrawing the eyepiece slightly and looking at a distance from the target. The anaesthetist may be asked to discontinue ventilation for some seconds while the bronchoscopist is at work. All blood must be removed to avoid lung collapse.

High sited tumours are difficult to manage because the tip of the bronchoscope lies between the cords.

Tumours involving a main bronchus. Since the growth obscures the lumen and sometimes involves the carina, it is often difficult to achieve accurate aim in the right plane. One should be careful and work slowly. In one patient we managed to clear a 2-cm passage without ever seeing the bronchial wall, but ended the procedure to avoid damage to the bronchus.

The anatomical boundary to be avoided (the cartilage) is the main problem. The bronchoscopist must balance caution and daring to attack the lesion, but he must not be overenthusiastic; it is a matter of judgment and training. Some structures are more dangerous, such as the pars membrana and those in relation with large vessels (aorta, inomminate artery). In our small series, we had no accidents involving either the oesophagus or a large vessel. The range of the beam is about 20 mm and only axial, but one must be careful to aim accurately.

It may be safer to avoid excessive therapy in one session and to repeat the procedure. After a time, charring prevents accurate demarcation of the tracheal wall, but the slough disappears after a few days. A control bronchoscopy and new session can then be performed safely. On many occasions we were pleasantly surprised to discover that the resection had been more complete than we expected, particularly in large tumours.

DISCUSSION

The introduction of the NdYAG laser provides a new concept in the management of tracheal and bronchial lesions. It enables the surgeon to treat tumours or stenosis sited deeply within the bronchial tree, either radically, or simply to relieve an obstruction. Some patients show signs of respiratory distress, and cannot withstand respiratory depression. The duration of the procedure is often unpredictable.

The technique described was found to be entirely satisfactory and there were no complications. It is too early yet to define the scope of this new technique, but it seems promising.

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CONDUITE ANESTHESIQUE DE LA CHIRURGIE TRACHEALE EN UTILISANT LE LASER NEODYMIUM–YTTRIUM–ALUMINIUM–GRENAT

RESUME

Une technique nouvelle destinée au traitement de lésions trachéales ou bronchiques (tumeurs ou sténoses) en utilisant le laser NdYAG sous couvert de bronchoscopie à été employée sur 55 malades sans complications. Nous analysons les problèmes anaesthésiques. Dans certains cas, l'opération peut se faire sous sédation et anesthésie de contact. Dans la plupart, nous avons utilisé l'anesthésie générale; la ventilation a été assurée par le bronchoscope, en utilisant une modifcation de l'injecteur de Sanders, avec un mélange de 50% d'azote et d'oxygène pour éviter le risque d'incendie.

ÜBER DIE BETÄUBUNG BEI TRACHELCHIRURGIE MITTELS NEODYMIUM–YTTRIUM–ALUMINIUM-GARNET-LASERS

ZUSAMMENFASSUNG

Eine neue Technik für die chirurgische Behandlung von Trachel- oder Bronchiallasionen (Tumoren oder Stenose) unter Anwendung des NdYAG-Lasers und der Bronchoskopie wurde bei 55 Patienten ohne Komplikationen verwendet. Die Narkoseprobleme werden beschrieben. Unter gewissen Umständen lasst sich das Verfahren unter Anwendung von Beruhigungsmitteln und einer ortlichen Betaubung verwenden. In den meisten Fällen wurde jedoch eine Allgemeinnarkose vorgezogen, wobei eine kontrollierte Ventilation durch das Bronchoskop unter Anwendung einer modifizierten Sanders-Injektors erreicht wurde, und einer Mischung von 50% Stickstoff und Sauerstoff verwendet wurde, um das Feuerrisiko zu verringern.

GERENCIA DE LA ANESTESIA PARA LAS OPERACIONES QUIRURGICAS TRAQUEALES USANDO EL LASER DE NEODIMIUM–YTRIUM–ALUMINIO–GARNET

SUMARIO

Se hizo uso de una técnica para la gerencia de lesiones traqueales o bronquiales (tumores o estenosis), usando el lase NdYAG y broncoscopia, en 55 paciente y sin complicación alguna. Se discuten los problemas anestésicos. En algunas circunstancias el procedimiento puede llevarse a cabo usando tranquilizantes o anestesia local. En la mayoría de estos casos, se usó anestesia general, lográndose la ventilación controlada a través del broncoscopio, haciendo uso de un inyector modificado de Sander con una mezcla de nitrógeno y de oxigeno al 50% con el fin de evitar el peligro de incendio

Br. J. Anaesth. (1980), 52, 999

EARLY EXTUBATION AFTER FONTAN OPERATION
A clinical report

J. L. Schuller, P. S. Sebel, J. G. Bovill and C. Marcelletti

SUMMARY

A report of early extubation after Fontan operation in nine patients is presented. All patients had a satisfactory course after operation with adequate Pa_{O_2} values. The possible benefits of early extubation are discussed.

Reports on management following cardiac surgery have emphasized the benefits of intermittent positive pressure ventilation (IPPV) in the period immediately after operation. Lefemine and Harken (1966) showed that IPPV decreased the frequency of hypoxia, acidosis, hypercarbia, hypotension and major atelectasis. Dammann and colleagues (1963) suggested that IPPV in the period immediately after operation should be routine. Peters, Wellons and Htwe (1969) demonstrated a considerable increase in the work of breathing after median sternotomy—an increase, however, that was most marked on the 3rd day after operation. This latter finding would suggest that the trachea may be extubated as safely immediately after surgery as later. More recent studies have explored this possibility. Prakash and others (1977) removed the tracheal tube in 82% of patients within 3 h of admission to the recovery room. Kaplan (1979) suggested that early extubation may contribute positively to patient care.

We felt that in certain instances there were positive benefits to be obtained from extubation immediately after operation, and this paper describes our clinical experience with early extubation after Fontan operation.

PATIENTS AND METHODS

The series comprised nine consecutive patients undergoing Fontan operation between August 1978 and June 1979. The age range was 6–37 yr and details of cardiological diagnosis and previous surgery are shown in table I.

All patients were premedicated with morphine 0.1 mg kg^{-1} and atropine 0.2–0.4 mg or hyoscine 0.2–0.4 mg except one patient (4) who received diazepam 0.15 mg kg^{-1} and hyoscine 0.2 mg.

Anaesthesia was induced with ketamine or methohexitone 2 mg kg^{-1} i.v. except in two children who requested gaseous induction. The children received cyclopropane 30–50% in oxygen followed by nitrous oxide in oxygen and halothane. The e.c.g. was monitored continuously during induction. Suxamethonium or pancuronium was administered to facilitate tracheal intubation. Two wide-bore i.v. cannulae, a central venous pressure catheter and a radial artery cannula were inserted percutaneously. In all patients the lungs were ventilated with nitrous oxide 40–50% in oxygen, supplemented with fentanyl. Intermittent halothane was used in two patients. During extracorporeal circulation ventilation was stopped and the lungs inflated with 3–5 cm H_2O continuous positive pressure. Cardiac arrest was achieved using St Thomas's cardioplegic solution at 4 °C and surgical correction was performed (table I). Valved conduits from Hancock or Carpentier–Edwards Laboratories were used.

After extracorporeal circulation, ventilation was restarted. Further increments of pancuronium and fentanyl were given as necessary. Packed cells, fresh frozen plasma and platelet concentrate were given for fluid replacement and control of haemostasis. When required an i.v. infusion of isoprenaline was used for inotropic support. Before closure of the chest, pleural and retrosternal drains were inserted. The anaesthetic requirements and duration of surgery are shown in table II.

At the end of surgery, the patients were allowed

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0007–0912/80/100999–06 $01.00

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TABLE I. *Detail of the patients. A = atrium/atrial; D = defect; L = left; P = pulmonary; R = right; S = septal; V = ventricle*

Patient	Age (yr)	Diagnosis before surgery	Previous cardiac surgery	Operative procedure
1	8	Tricuspid atresia, ASD, VSD, pulmonary stenosis	Waterston shunt age 1	Take down Waterstone. Closure ASD, VSD. Conduit from RA to RV and PA
2	9	Criss cross heart, pulmonary stenosis	Blalock–Hanlon operation + central shunt age 9 not working	Glenn anastomosis, ventricular exclusion. Conduit RA to LPA
3	8	Tricuspid atresia, ASD, VSD		Closure ASD, VSD. Conduit RA to RV
4	6	Mirror image dextrocardia, complete endocardial cushion defect, infundibular pulmonary stenosis, hypoplastic LV		Closure ASD, ventricular exclusion. Conduit RA to PA
5	11	Univentricular heart, main chamber LV type, pulmonary stenosis	Blalock shunt age 8	Closure ASD, ventricular exclusion. Conduit RA to PA
6	12	Tricuspid atresia, ASD, VSD	Glenn anastomosis age 9 months	Closure ASD, VSD. Conduit RA to rudimentary RV and PA
7	14	Tricuspid atresia, ASD, VSD	Blalock shunt age 1, non-functioning. Glenn anastomosis age 4, functioning	Closure ASD, VSD resection infundibular septum. Enlargement LPA. Conduit RA to RV
8	37	ASD, VSD, Ebstein malformation with stenotic tricuspid valve		Closure ASD, VSD Conduit RA to RV
9	18	ASD, VSD, tricuspid atresia	Glenn anastomosis age 10 months, functioning	Closure ASD, VSD. Conduit RA to rudimentary RV and LPA

to breathe oxygen 100% through a Mapleson C system. Atropine and neostigmine were administered to one patient (1).

After surgery, the trachea was extubated if there was no excessive bleeding and the patient was able to open the eyes to command and was breathing adequately (no paradoxical respiration, no excessive use of accessory muscles and no clinical signs of carbon dioxide retention).

The patients were transferred to the intensive care unit, where oxygen 5 litre min^{-1} was given via a face-mask. The retrosternal drains were removed on the day after surgery and the pleural drain left for at least 7 days. Diuretics were given after operation as required. All patients received prophylactic antibiotic therapy.

RESULTS

Using the criteria described above, the endotracheal tubes were removed in all patients, in the operating theatre, within 20 min of the end of surgery except for one patient (5) in whom the tube was retained and oxygen was given via a T-piece for 2 h, by which time the patient was judged to be adequately awake and his trachea was extubated. Table III shows details of Pa_{O_2} values during and after surgery.

In all patients the first Pa_{O_2} value measured after surgery, taken shortly after return to the intensive care unit, was greater than the pre-bypass Pa_{O_2} when the lungs were being ventilated artificially. Patients nos 6 and 9 both had Pa_{O_2} values less than 7 kPa on the morning following operation. Both had had previous Glenn anastomoses. Patient 5 had low Pa_{O_2} values from the 4th to the 8th day following surgery. These were associated with peritoneal dialysis.

Mean values for [H$^+$], Pa_{CO_2} and base excess are shown in table IV.

All Pa_{CO_2} values in the first 24 h after surgery were less than 6.65 kPa (50 mm Hg). After operation all patients developed some degree of pleural

TABLE II. *Anaesthetic details*

Patient	Wt (kg)	Induction agent (mg)	Suxamethonium (mg)	Total dose pancuronium (mg kg^{-1})	Time before end surgery to last pancuronium (h)	Total dose fentanyl (μg kg^{-1})	Time before end surgery to last fentanyl (h)	Duration extracorp. circ. (min)	Duration surgery (h)	Other anaesthetic agents used
1	28.4	Cyclopropane/O_2 $\rightarrow N_2O/O_2$ halothane		0.21	1.5	10	1.5	119	4.7	Halothane Atropine 0.5 mg Neostigmine 1.0 mg
2	28	Ketamine 60		0.21	4	17	4	162	7.5	
3	26	Ketamine 40	25	0.21	1.5	7	1.75	103	4	
4	33.5	Methohexitone 70	30	0.22	4	9	0.5	132	5.5	
5	36.8	Ketamine 75		0.16	1.25	8	0.5	119	4.75	
6	32	Cyclopropane/O_2 $\rightarrow N_2O/O_2$ Halothane		0.12	4.5	7	4.5	117	4	
7	42	Ketamine 75	50	0.19	2	12	2	137	6	Halothane
8	57	Methohexitone 35		0.17	4	7	0.5	97	5.75	
9	50	Ketamine 100	50	0.16	4	4	5	119	5	

TABLE III. *Pa_{O_2} values (kPa) during and after surgery*

	During operation, on ventilator				After operation, breathing spontaneously		
	Before extra-corporeal circ.		After extra-corporeal circ.				
Patient	Pa_{O_2}	FI_{O_2}	Pa_{O_2}	FI_{O_2}	1st measured Pa_{O_2}	1st sample next day	Last sample taken in ICU
1	8.51	45	17.29	35	28.87	30.86	24.21
2	7.58	40	16.63	60	14.50	12.10	14.50
3	8.51	50	28.33	50	24.21	8.25	8.11
4	8.51	50	7.18	50	16.76	26.33	12.90
5	6.38	50	55.99	100	20.22	7.85	11.97
6	6.91	50	13.97	50	8.78	6.12	6.12
7	5.72	50	28.46	45	14.90	23.41	10.10
8	7.45	42	26.33	36	18.35	17.56	15.03
9	7.05	50	35.24	50	7.84	6.52	9.04

TABLE IV. *$[H^+]$, Pa_{CO_2} and base excess data (mean ± SD). Range in parentheses*

	$[H^+]$ (nmol litre^{-1})	Pa_{CO_2} (kPa)	Base excess (mmol litre^{-1})
Before extracorporeal circulation	39.26 ± 4.82 (32.5–51.2)	4.47 ± 0.78 (3.72–6.38)	−2.66 ± 1.61 (−6.5 to −0.5)
After extracorporeal circulation	39.57 ± 5.21 (34.6–51.2)	4.30 ± 1.52 (3.86–6.57)	−2.72 ± 2.34 (−7.5 to +1)
1st sample after operation	44.71 ± 5.68 (38.9–58.8)	5.33 ± 0.78 (4.12–6.52)	−3.00 ± 2.94 (−8 to 0)
1st sample next day	35.52 ± 5.55 (31.6–42.6)	5.55 ± 0.48 (4.65–6.25)	+4.00 ± 3.35 (0.5 to +11)
Last measured sample in intensive care unit	34.87 ± 3.06 (29.5–38.9)	5.58 ± 0.80 (3.59–6.38)	+5.00 ± 3.85 (−1.5 to +10.5)

TABLE V. *Complications after operation*

Patient	Complication(s)
1	Flaccid tetraparesis for several months. Completely recovered
2	Required permanent pacemaker after operation
3	Sternal infection
4	Haemodialysis from 12th to 15th day after operation. Serum creatinine again normal from 29th day
5	Peritoneal dialysis from 4th to 8th day, with signs of cerebral oedema from 4th to 10th day after operation. Complete recovery from cerebral oedema. No neurological deficit from 30th day. Serum creatinine normal from 17th day
6	None
7	None
8	None
9	Repeat thoracotomy for bleeding 2 h after operation, followed by extubation immediately after re-operation

effusion and ascites of variable duration. The other complications which followed surgery are summarized in table V.

At the last follow-up examination, eight patients were well with a good exercise tolerance. Patient 2 showed no improvement in exercise tolerance after surgery but patient 5, who had developed cerebral oedema, can now ride a bicycle.

DISCUSSION

Following Fontan operation the venous pressure becomes the driving force for pulmonary blood flow. Shemin and others (1979) have shown, in dogs with artificially-induced tricuspid atresia and a right atrial to pulmonary artery conduit, that the right atrium does not function as a pump to maintain pulmonary blood flow. For the pulmonary circulation to function effectively, venous pressure must be kept sufficiently great to provide adequate conduit flow. Complications that may occur with a continuous high venous pressure are pleural effusion, ascites, liver and renal failure and cerebral oedema. Therefore, in such patients the smaller mean intrathoracic pressure resulting from spontaneous ventilation compared with that following positive pressure ventilation should permit better pulmonary perfusion with a smaller venous pressure.

Extensive information about ventilatory management after Fontan operation is lacking. Gale and colleagues (1979) could extubate all but three patients within 48 h of surgery in a series of 17 Fontan operations for univentricular heart and other complex congenital anomalies. All their patients were in a labile haemodynamic state for 24 h after operation and needed high venous pressures with inotropic support. In their series, three patients required peritoneal dialysis, two of whom died. Bilateral pleural effusions and ascites were present in all patients. They considered that there was a relationship between preoperative pulmonary vascular resistance and postoperative course.

Theoretically, extubation immediately after surgery should reduce the complications caused by increased venous pressure. In our series there were three patients with a single ventricle or other complex congenital anomaly. Two of these developed renal failure probably related to a low cardiac output. One was treated with haemodialysis, the other with peritoneal dialysis. This last patient showed signs of cerebral oedema during the period of renal failure; both patients recovered. All nine patients showed some degree of pleural effusion and ascites. Two of the three patients who had a previous Glenn anastomosis had low Pa_{O_2} values after surgery. We speculate that these patients may have had some degree of pulmonary venous to arterial shunting which is known to occur after Glenn anastomosis (McFaul et al., 1977).

In a review of 1065 operations for the creation of an extracardiac conduit one of us (C. M., unpublished) found an early mortality of 17 out of 97 for tricuspid atresia and 29 out of 76 for univentricular heart. In our series there was no mortality.

Early extubation after Fontan operation does not eliminate the complications of high venous pressure, but we would suggest that it is a reasonably safe procedure with theoretical benefits for the patient.

APPENDIX

Fontan operation. As originally described by Fontan and Baudet (1971), a Glenn anastomosis and right atrium to right pulmonary artery anastomosis using an aortic valve homograft. Modified operation uses a valved conduit.

Glenn anastomosis. End-to-side anastomosis of distal end of right pulmonary artery to superior vena cava.

Blalock–Taussig anastomosis. Subclavian artery to right or left pulmonary artery.

Waterston shunt. Ascending aorta to right pulmonary artery.

Blalock–Hanlon operation. Atrial septectomy

Ventricular exclusion. Patch closure of right atrio-ventricular valve with closure of atrial septal defect.

Central shunt. Aorta to pulmonary artery.

ACKNOWLEDGEMENTS

We would like to thank Professor N. G. Meijne and his staff, Drs G. Losekoot, J. Lam, J. L. Beiboer, L. Thompson-Hill and H. Olthof for their help and co-operation.

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DETUBAGE PRECOCE APRES UNE OPERATION DE FONTAN

Rapport clinique

RESUME

On présente dans ce document un rapport sur le détubage précoce de neuf patients après une opération de Fontan. Tous les patients ont eu une récupération satisfaisante après l'opération et la valeur de leur Pa_{O_2} a été adéquate. Les avantages éventuels du détubage précoce y sont débattus.

FRÜHE EXTUBATION NACH FONTAN-OPERATION

Ein Klinischer Bericht

ZUSAMMENFASSUNG

Ein Bericht über frühe Extubation nach einer Fontan-Operation an 9 Patienten wird vorgelegt. Alle Patienten nahmen nach der Operation einen befriedigenden Verlauf mit ausreichenden Werten von Pa_{O_2}. Die moglichen Vorteile einer frühen Extubation werden diskutiert.

EXTUBACION TEMPRANA DESPUES DE UNA OPERACION FONTAN

Un informe clínico

SUMARIO

Se presenta un informe sobre extubacion temprana después de una operación Fontan. Todos los pacientes siguieron un curso satisfactorio después de la operación con valores de Pa_O adecuados. Se discuten los posibles beneficios de la extubación temprana.

Br. J. Anaesth. (1980), 52, 1005

ANOTHER LOOK AT ACUTE TOLERANCE TO THIOPENTONE

W. TONER, P. J. HOWARD, W. A. W. MCGOWAN AND J. W. DUNDEE

SUMMARY

The phenomenon of "acute tolerance" to thiopentone was re-examined in 82 subjects with induction doses of 2–15 mg kg^{-1}. There was a strong positive correlation between the venous plasma thiopentone concentrations on recovery from anaesthesia and the induction dose, expressed as either mg kg^{-1} or mg m^{-2}. Recovery time was proportionately shorter with larger doses, being directly related to $\log_{10}$ of the plasma concentration at awakening.

There is great individual variation in the response to thiopentone, including the dose required to induce anaesthesia and the plasma concentration at which patients recover consciousness. The work of Brodie (1952) clarified the latter; each of four subjects was infused with two different doses and it was seen (table I) that the plasma concentration at recovery was greater when the larger dose of drug was given. These doses are outside the range used today, but Dundee, Price and Dripps (1956) described a phenomenon which they called "acute tolerance" to thiopentone. In 16 subjects given single doses of thiopentone ranging from 2 to 12 mg kg^{-1} they found that patients receiving the larger doses awakened at a greater arterialized venous plasma concentration of the drug than those given smaller doses.

TABLE I. *Plasma concentrations at wakening in four subjects each infused with two doses of thiopentone. From Brodie (1952).*

	Thiopentone	
Subject	Dose (mg kg^{-1})	Plasma concn at wakening (µg ml^{-1})
V	59	32.6
	36	22.6
M	67	27.8
	40	19.3
G	43	19.8
	22	13.2
N	50	26.0
	33	16.8

With the availability of modern and less time-consuming analytical techniques (Toner et al., 1979) a further, more comprehensive examination of the phenomenon of acute tolerance was undertaken in 82 unselected, unpremedicated adults. The dose of thiopentone ranged from 2 to 15 mg kg^{-1} and venous blood was used for analysis. The findings of this study have been summarized by Dundee (1980) and Dundee and others (1980).

METHODS

Doses were allocated at random and injected rapidly over 2–5 s. The time was noted from injection to recovery (open eyes on command). In some patients the thiopentone was given well in advance of operation, the time to recovery was noted and anaesthesia was reinduced with nitrous oxide in oxygen and a further small dose of barbiturate. With larger doses a short operation was carried out during nitrous oxide in oxygen anaesthesia, but nitrous oxide was discontinued immediately and recovery usually took a further 3–5 min. Immediately on waking a venous blood sample (for thiopentone analysis) was drawn from the arm opposite to that used for injection. Plasma thiopentone concentration was estimated using an Anachem High Performance Liquid Chromatograph fitted with a fixed wavelength ultra-violet light detector (254 nm) with sensitivity set at 0.08. A reverse phase (15 cm × 0.3 cm i.d.) spherisorb 10 ODS column and a mobile phase of methanol–water 50 : 50 at a pressure of 7000 kPa was used (Toner et al., 1979).

In presenting the data, the dose of thiopentone is expressed as mg kg^{-1} except in figure 2. Student's

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0007-0912/80/101005-04 $01.00

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t-test and linear regression analyses were used as required.

RESULTS

Eighty-two patients were studied. The relationship between the plasma thiopentone concentration at awakening and the dose administered (mg kg^{-1}) is shown in figure 1. There was a positive linear relationship between these two factors ($r = 0.694$). With the dose expressed as mg m^{-2}, a similar relationship was shown with a correlation value of $r = 0.654$ (fig. 2). Hereafter, the dose will be expressed as mg kg^{-1}.

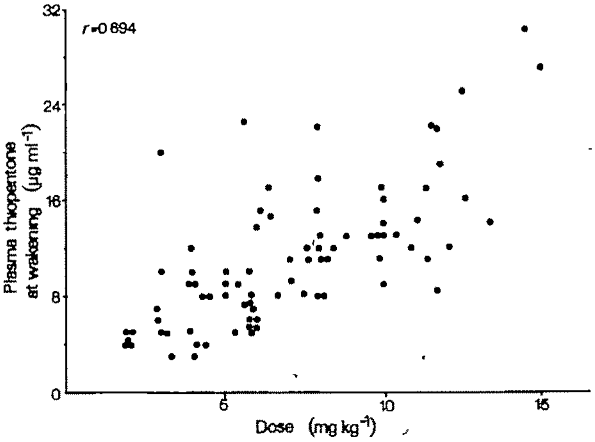

FIG. 1. Relationship between dose of thiopentone (mg kg^{-1}) and venous plasma concentration at wakening (µg ml^{-1}).

Figure 3 groups the doses of thiopentone and table II shows the significance of the difference of average plasma concentrations in the thiopentone groups. Table II also shows average times to wakening and the significance of difference between groups.

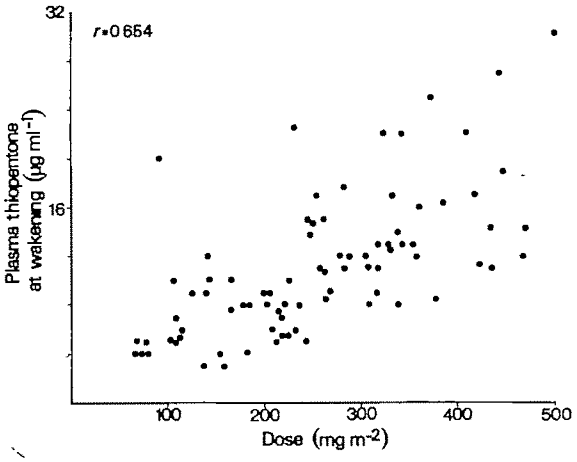

FIG. 2. Relationship between dose of thiopentone (mg m^{-2}) and venous plasma concentration at wakening (µg ml^{-1}).

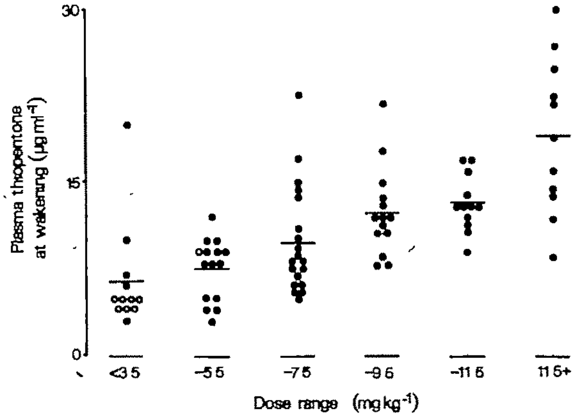

FIG. 3. Data as for figure 1 divided into six groups. ● = Individual patients; —— = mean of groups; ○ = patients who did not go to sleep.

In the group receiving less than 3.5 mg kg^{-1}, seven patients did not go to sleep, but samples

TABLE II. *Grouped data on average plasma thiopentone concentrations at wakening, and average recovery times in each group. †Seven patients did not sleep; *one patient did not sleep*

Dose (mg kg^{-1})	*n*	Average plasma thiopentone concn at wakening (µg ml^{-1} ± SEM)	*P*	Average time to wakening (min ± SEM)	*P*
<3.5	12†	6.5 ± 1.3	<0.5	2.75 ± 0.8	<0.05
3.5–5.5	15*	7.6 ± 0.7	<0.1	5.2 ± 0.9	<0.01
5.5–7.5	19	9.9 ± 1.1	<0.2	8.4 ± 0.6	<0.9
7.5–9.5	14	12.5 ± 1.0	<0.5	8.6 ± 1.0	<0.1
9.5–11.5	12	13.3 ± 0.7	<0.01	11.3 ± 1.2	<0.5
11.5+	11	19.1 ± 2.0		13.6 ± 3.1	

were taken between 1 and 2 min after injection; this also applies to one patient in the group receiving 3.5–5.5 mg kg^{-1}. These concentrations were less than those of the patients who went to sleep ($P < 0.1$).

Although averages of plasma concentrations and wakening times between consecutive groups were not significantly different (table II), a highly significant ($P < 0.02$) difference was found between alternate groups. There was a less marked correlation ($r = 0.56$) between the dose of thiopentone and time to recovery.

However, using the grouping of doses shown in figure 3, a very good correlation ($r = 0.98$) between $\log_{10}$ average plasma thiopentone concentration on wakening and the average recovery time was obtained (fig. 4).

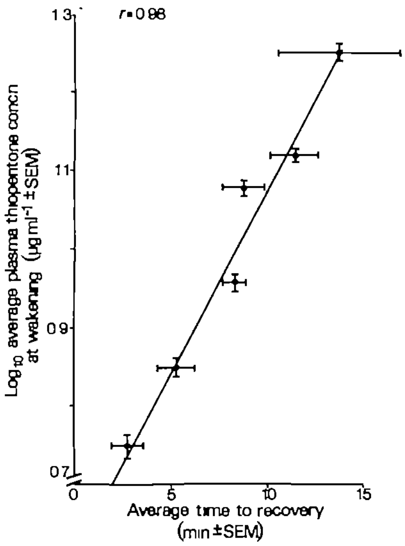

FIG. 4. Relationship between $\log_{10}$, average plasma thiopentone concentrations at wakening (µg ml^{-1}) and average time to wakening (min).

DISCUSSION

A comparison of figures 1 and 2 suggests that there is little advantage in using mg m^{-2} as a means of expressing the dose of thiopentone rather than the more commonly used mg kg^{-1}.

This paper does not elucidate the mechanism of the phenomenon of acute tolerance. The present study confirms the relationship found in the smaller series of Dundee, Price and Dripps (1956). Although the correlation coefficient in the earlier data was 0.74, based on only 16 patients, this compared favourably with $r = 0.694$ in the 82 patients. One may question the validity of venous concentrations of thiopentone, but generally the blood was sampled 4–5 min after induction and by that time the difference between arterial and venous concentration should be negligible.

This study further substantiates the view that plasma thiopentone concentration is a poor guide to the depth of anaesthesia; the findings regarding concentrations at recovery support those of the previous study by Dundee, Price and Dripps (1956) and that by Brand and others (1961) who found no correlation between plasma thiopentone concentrations and the "depth" of anaesthesia as judged by the electroencephalogram.

The medico–legal implications of this finding are obvious. Serial plasma concentrations may be a guide to the depth of anaesthesia and to the speed of recovery, but isolated concentrations are meaningless.

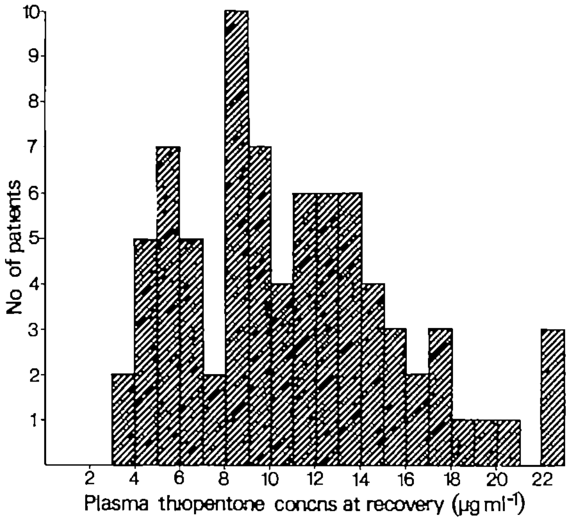

FIG. 5. Scatter of venous thiopentone concentrations at wakening.

Figure 5 shows the distribution of plasma concentrations of thiopentone at the time of recovery in these 82 patients. Undoubtedly the phenomenon of "acute tolerance" is a major factor in this scatter.

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EXAMEN COMPLEMENTAIRE DE L'ACCOUTUMANCE AIGUE AU THIOPENTONE

RESUME

On a à nouveau examiné le phénomène de l'accoutumance aigüe au thiopentone sur 82 sujets, en utilisant des doses d'induction de 2–15 mg kg^{-1}. On a constaté une forte corrélation positive entre les concentrations de thiopentone dans le plasma veineux au moment de la reprise de conscience, après l'anesthésie, et la dose d'induction, exprimée soit en mg kg^{-1} soit en mg m^{-2}. Le temps nécessaire à la reprise de conscience a été proportionnellement plus court avec les doses les plus impotantes, celui-ci étant directement relié au $\log_{10}$ de la concentration dans le plasma au moment du réveil.

EINE WEITERE BETRACHTUNG DER AKUTEN TOLERANZ FÜR THIOPENTON

ZUSAMMENFASSUNG

Das Phänomen der akuten Toleranz auf Thiopenton wurde bei 82 Personen mit Narkosedosen von 2–15 mg kg^{-1} neu untersucht. Es besteht eine starke positive Verbindung zwischen den venösen Plasma-Thiopentonkonzentrationen nach Aufwachen aus der Narkose und der Narkosedosis, ausgedrückt entweder in mg kg^{-1} oder in mg m^{-2}. Die Erholungszeit war proportional kürzer mit grösseren Dosen und stand in direktem Zusammenhang zu $\log_{10}$ der Plasmakonzentration beim Erwachen.

UN NUEVO EXAMEN DE LA TOLERANCIA AGUDA A LA TIOPENTONA

SUMARIO

El fenómeno de "tolerancia aguda" a la tiopentona se volvió a examinar en 82 pacientes mediante dosis de inducción de 2–15 mg kg^{-1}. Tuvo lugar una fuerte correlación positiva entre las concentraciones de tiopentona en el plasma venoso al recuperarse de la anestesia y la dosis de inducción, expresada bien en mg kg^{-1} o en mg m^{-2}. El tiempo de recuperación fue proporcionalmente más corto para las mayores dosis, viniendo relacionado directamente al $\log_{10}$ de la concentración de plasma al momento de despertar.

Br. J. Anaesth. (1980), 52, 1009

COMPARATIVE STUDY OF THE CLINICAL EFFECTS OF TOFIZOPAM, NITRAZEPAM AND PLACEBO AS ORAL PREMEDICATION

A. Pakkanen, J. Kanto, L. Kangas and M. Mansikka

SUMMARY

In a double-blind randomized study 47 patients received tofizopam 100 mg orally the night before operation, and 100 mg on the morning of operation; 49 patients received nitrazepam 5 mg and 50 patients received placebo. On average the nitrazepam group slept better and were better sedated than the tofizopam or placebo groups. Compared with placebo or nitrazepam, tofizopam decreased the excitement of the patients. The effect of tofizopam on apprehension and excitement was significantly better than those of placebo or nitrazepam. Nitrazepam, but not tofizopam, significantly decreased the induction requirements of thiopentone.

In this study we have compared the clinical effects of tofizopam with those of nitrazepam and a placebo. Nitrazepam, a 7-nitrobenzodiazepine, has prominent sedative and hypnotic effects; it also has anxiolytic, muscle-relaxing, anticonvulsant and amnesic properties, all of which are beneficial when it is used as an oral premedicant (Dundee and Haslett, 1970; Kangas, Kanto and Mansikka, 1977). Tofizopam is a relatively new benzodiazepine derivative (1-(3,4-dimethoxy-phenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine), with a distinct anxiolytic effect. However, it differs from other benzodiazepines in having, apparently, no sedative properties (Petöcz and Kosóczky, 1975; Várady, Bolla and Sebö, 1975).

PATIENTS AND METHODS

In this double-blind study three groups of patients received, in random order, tofizopam 100 mg (two tablets of Grandaxin, test preparation, Farmos Group Ltd, Turku, Finland, each containing tofizopam 50 mg) (group 1, $n = 47$), nitrazepam 5 mg (one tablet of Somitran, Medipolar, Oulu, Finland, and one placebo tablet) (group 2, $n = 49$) or two placebo tablets (group 3, $n = 50$), orally at 9 p.m. on the night before operation and at 7 a.m. on the following morning. Mean ages, weights and heights of the patients were 42.6 ±13.6 (SD) yr, 66.4±10.7 kg and 165.6±7.9 cm in group 1; 39.7±14.9 yr, 67.6±10.2 kg and 166.0±6.7 cm in group 2; 39.1±11.8 yr, 66.1±10.2 kg and 166.9±8.2 cm in group 3. The patients were in good general health (ASA class 1, except for one patient in group 3 and two patients in group 1 and 2 who were ASA class 2). About half of each group were gynaecological inpatients and the other half e.n.t. inpatients (males and females in equal numbers; there were no significant differences between the three groups in this respect).

The subjective and objective assessments before operation (carried out by M.M. in gynaecological patients and A.P. in e.n.t. patients) were recorded in the operating room, as suggested by Dundee, Moore and Nicholl (1962) with minor modifications as presented in our earlier studies (Kangas, Kanto and Mansikka, 1977; Kanto et al., 1979, 1980; Mansikka et al., 1979; Mansikka, Kangas and Kanto, 1980). The mean time interval between the second dose of the drug and the assessment was 2.74±1.38 (SD) h in group 1, 2.90±1.62 h in group 2 and 2.65±1.34 h in group 3. Thiopentone was given as an i.v. induction agent until loss of the eyelid reflex, the dose ($mg\ kg^{-1}$) being recorded in order to test the sedation produced by the three different premedicants. The statistical analyses of the results were carried out with χ^2-test and Student's t test.

RESULTS

Patients in the nitrazepam group slept significantly better and were more sedated than those in the

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0007-0912/80/101009-04 $01.00

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TABLE I. *Effects of tofizopam, nitrazepam and placebo on various indices (per cent of patients reporting each effect) with significant differences from placebo (*P<0.05, **P<0.01) or from nitrazepam (†P<0.01)*

	Tofizopam (%)	Nitrazepam (%)	Placebo (%)
Sleep			
good	36	74	38
fair	36†	18**	36
poor	28	8	26
Sedation			
marked	8	14	6
moderate	26†	45**	26
slight	28	31	36
nil	38	10	32
Apprehension			
absent	68	61	54
slight	23	27	20
moderate	9	12	22
marked	0	0	4
Excitement			
nil	47	33	20
slight	42*	51	60
moderate	11	16	18
marked	0	0	2
Dizziness			
nil	94	84	92
slight	6	16	8
marked	0	0	0
Emetic effect			
nil	87	94	82
slight nausea	11	6	14
severe nausea	2	0	0
vomiting	0	0	4
Headache			
nil	55	59	46
slight	32	35	44
severe	13	6	10

tofizopam or placebo groups (table I). The patients receiving tofizopam were less anxious than those receiving placebo ($P<0.05$). When the results of the "anxiolytic effect" (apprehension and excitement) were combined the difference between tofizopam and placebo was even more marked ($P<0.001$); there were no significant differences between placebo and nitrazepam or nitrazepam and tofizopam. Tofizopam did not improve sleep on the night before operation and had no sedative effect when compared with placebo. The mean induction dose of thiopentone was 4.53 ± 1.15 (SD) mg kg^{-1} in group 1, 4.25 ± 1.07 mg kg^{-1} in group 2 and 4.79 ± 1.11 mg kg^{-1} in group 3. Groups 2 and 3 (nitrazepam, placebo) differed significantly from each other ($P<0.05$). There were no significant differences between the three groups in respect of cardiovascular indices (table II).

DISCUSSION

In animal experiments performed on different species, tofizopam has proved to be a tranquillizer with almost no sedative or sleep-inducing properties. Furthermore, it had no muscle-relaxing or anticonvulsant effects, and its lack of cardiovascular effect in animals suggest that it may be of therapeutic value in angina (Petöcz and Kosóczky, 1975). In contrast to other tranquillizers, tofizopam has a clinical anxiolytic effect without producing fatigue or day-time sleepiness; indeed, the drug seems to have a mild stimulant rather than sedative action (Várady, Bolla and Sebõ, 1975; Gerevich et al., 1975). In myasthenic or myopathic patients it had no muscle-relaxing activity (Szobor, 1975), and it decreased the psychological symptoms in patients at the menopause (Csillag et al., 1975).

Our results have shown that tofizopam produced an anxiolytic effect without sedative or sleep-inducing actions. Generally, it is not easy to separate clearly the anxiolytic effect of the benzodiazepines from their sedative effect (Dundee and Haslett, 1970), although in a previous study we were able to differentiate, to some extent, sedative and anxiolytic effects of flunitrazepam (Kanto, Kangas and Mansikka, 1980).

Nitrazepam decreased significantly apprehension and excitement in inpatients compared with outpatients without premedication (Kangas, Kanto and Mansikka, 1977). The good sedative effect of nitrazepam was observed again, in this study and a smaller dose of thiopentone was required to induce anaesthesia in comparison with placebo.

The prominent anxiolytic effect of tofizopam and lack of sedative properties are of great clinical importance. In anaesthetic practice it could be of value in the premedication of outpatients. In our earlier studies the beneficial properties of the benzodiazepines, as oral premedicants, included minimal cardiovascular effect, easy venepuncture and a low frequency of headache (Kangas, Kanto and Mansikka, 1977; Kanto, Kangas and Mansikka, 1980; Mansikka et al., 1979). In this study, however, tofizopam had no particular extra advantage. The sedative effect of the benzodiazepine derivatives may protect against cardiovascular and autonomic reactions during surgery.

TABLE II. *Effects of tofizopam, nitrazepam and placebo on cardiovascular variables (percent of patients reporting each effect)*

	Tofizopam (%)	Nitrazepam (%)	Placebo (%)
Increase in systolic arterial pressure			
no change (0–20 mm Hg)	65	71	73
moderate (21–40 mm Hg)	33	22	23
severe (>40 mm Hg)	2	7	4
Decrease in systolic arterial pressure			
no change (0–20 mm Hg)	96	92	94
moderate (21–40 mm Hg)	4	8	4
severe (>40 mm Hg)	0	0	2
Heart rate (beat $\min^{-1}$)			
100	91	92	90
100–120	9	8	10
121–140	0	0	0
>140	0	0	0
Venepuncture			
easy	77	73	64
moderately easy	19	27	30
difficult	4	0	6

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ETUDE COMPARATIVE DES EFFETS CLINIQUES DU TOFIZOPAM, DU NITRAZEPAM ET D'UN PLACEBO ADMINISTRES PAR VOIE BUCCALE EN TANT QUE MEDICAMENTS PRE-OPERATOIRES

RESUME

Au cours d'une étude á double inconnue effectuée au hasard, il a été administré par voie buccale à 47 patients 100 mg de tofizopam, le soir qui a précédé le jour de l'opération et 100 mg le matin même du jour de l'opération; 49 patients ont reçu 5 mg de nitrazépam et 50 autres, un placébo. Dans l'ensemble, le groupe soumis au nitrazépam a mieux dormi et était plus reposé que les groupes ayant reçu du tofizopam ou un placébo. Par rapport au placébo et au nitrazépam, le tofizopam a fait baisser l'excitation des patients. Les effets du tofizopam sur l'appréhension et l'excitation ont été nettement meilleurs que ceux du placébo ou du nitrazépam. Le nitrazépam, mais pas le tofizopam, a nettement fait baisser les exigences d'induction du thiopentone.

VERGLEICHENDE STUDIE DER KLINISCHEN EFFEKTE VON TOFIZOPAM, NITRAZEPAM UND PLAZEBO ALS KLINISCHE VORBEHANDLUNG

ZUSAMMENFASSUNG

In einer willkürlichen Doppelblindstudie erhielten 47 Patienten oral 100 mg Tofizopam in der Nacht vor der

Operation, und 100 mg am Morgen der Operation. Neunundvierzig Patienten erhielten 5 mg Nitrazepam, und 50 Patienten eine Plazebodosis. Die Nitrazepamgruppe schlief durchschnittlich besser und war durchschnittlich besser sediert als die beiden anderen. Im Vergleich zu Plazebo oder Nitrazepam senkte Tofizopam die Erregung der Patienten, mit einer diesbezüglich deutlich besseren Wirkung als Plazebo oder Nitrazepam. Nitrazepam—nicht aber Tofizopam—verringerte die Narkosedosis von Thiopenton wesentlich.

ESTUDIO COMPARATIVO DE LOS EFECTOS CLINICOS DE TOFIZOPAM, NITRAZEPAM Y DE PLACEBO COMO PREMEDICACION ORAL

SUMARIO

En un estudio aleatorizado de doble anonimato, 47 pacientes recibieron oralmente 100 mg de tofizopam la noche anterior a la operación, y otros 100 mg en la mañana del dia correspondiente a la operación; 49 pacientes recibieron 5 mg de nitrazepam y otros cincuenta recibieron un placebo. Por termino medio, el grupo que recibió nitrazepam durmió mejor y estuvo más calmado que los que recibieron tofizopam o el placebo. En comparación con el placebo o el nitrazepam, el tofizopam disminuyó la excitación de los pacientes. El efecto de tofizopam sobre la aprensión y excitación de los pacientes fue significativamente mejor que el del placebo o el del nitrazepam. El nitrazepam disminuyó de forma significativa los requisitos de inducción de la tiopentona, no siendo esto asi en el caso del tofizopam.

Br. J. Anaesth. (1980), 52, 1013

CLINICAL EFFECTS OF BUPRENORPHINE DURING AND AFTER OPERATION

H. J. McQuay, R. E. S. Bullingham, G. M. C. Paterson and R. A. Moore

SUMMARY

The analgesic, respiratory and hormonal effects of two doses of buprenorphine were studied during and after operation in 20 patients undergoing total hip replacement. The drug provided analgesia of long duration. The analgesic and hormonal effects of the drug were greater after i.m. than after i.v. administration The postoperative analgesic requirement of women was less than that of men. The pharmacodynamic differences shown between the sexes and between the two routes of administration are discussed in relation to the pharmacokinetics of the drug.

Buprenorphine is a synthetic opiate analgesic with mixed agonist–antagonist properties and a low abuse potential (Heel et al., 1979). It has unusual receptor kinetics (Hambrook and Rance, 1976), and in clinical use has been shown to provide analgesia of long duration. This study was designed to determine the pharmacokinetics of buprenorphine in man when injected by either the i.v. or i.m. route, and to compare the i.v. pharmacokinetics in the same patient in both the anaesthetized and awake conditions (Bullingham et al., 1980). A secondary aim was to collect data on the analgesic effects of the drug, together with its effects on respiratory depression, plasma glucose concentration and endocrine function, and it is these results which are presented.

The inadequacy of existing regimens of analgesia after operation has been widely stressed (Keeri-Szanto and Heaman, 1972). Claims of prolonged action for any new analgesic merit careful assessment of analgesia; in this study patient-controlled demand analgesia was used.

A postoperative analgesic which provided long-lasting pain relief at the expense of unacceptable respiratory depression would have no advantage and, therefore, arterial blood-gas tensions were measured after operation.

It has been proposed that reduction of the stress response to surgery may be beneficial to the patient (Kehlet, 1979), and hormone and blood glucose concentrations have been measured to investigate the effects of buprenorphine on the stress response during and after operation.

PATIENTS AND METHODS

Ethics Committee approval was obtained for this study on patients undergoing elective total hip replacement at the Nuffield Orthopaedic Centre, Oxford. Twenty patients were divided into two groups, V and M, with six men and four women in each group. Both groups were given a first dose of buprenorphine i.v. at the induction of anaesthesia. Group V received a second dose of buprenorphine i.v. Group M received a second dose i.m. Patients were selected sequentially from operation lists if their age was between 45 and 75 yr and their weight less than 80 kg. Those with serious medical disorders or those taking antihypertensive drugs other than thiazides were excluded. A normal full blood count and biochemical examination before operation were conditions of entry to the trial. Signed consent to the study was obtained from each subject.

The patients were premedicated with diazepam 10 mg orally 2 h before surgery. A 1.6-mm i.d. cannula (Venflon) was inserted into an arm vein under local analgesia. All patients received thiopentone 4 mg kg^{-1} and pancuronium 0.1 mg kg^{-1}. After tracheal intubation the lungs were ventilated with oxygen 33% in nitrous oxide and halothane 0.5% from a Fluotec Mk2 vaporizer. Ventilation to normocapnia was achieved using the Penlon version of the Bain co-axial breathing circuit with a total fresh gas flow of 70 ml kg^{-1}. The ventilator was adjusted to pro-

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0007-0912/80/101013-07 $01.00

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duce an expired tidal volume (measured at the endotracheal catheter connector) of 10 ml kg^{-1} and respiratory frequency of 13 b.p.m. A 0.53-mm i.d. cannula (Longdwell) was inserted into the radial artery. Buprenorphine 0.3 mg diluted to 10 ml with normal saline was injected i.v. over 1 min.

Halothane 0.5% was continued until 10 min before antagonism of the neuromuscular blocking drug. Halothane was used to avoid any possibility of awareness and to suppress any autonomic effects which might have influenced the drug kinetics. No increment of any drug was given. All patients lay on warming blankets and direct arterial pressure, heart rate, rectal temperature and e.c.g. were monitored during anaesthesia. During anaesthesia 5 ml kg^{-1} h of Hartmann's solution was given i.v. for the first 2 h, and thereafter blood was transfused to a specific plan depending on the preoperative haemoglobin concentration, and blood loss assessed by swab weighing and suction.

At the end of surgery the anaesthetic gases were discontinued and residual neuromuscular blockade was antagonized with atropine 1.2 mg and neostigmine 2.5 mg i.v. The patients were transferred to the recovery room, and remained there until the following morning. All patients remained supine and breathed oxygen 28% from a Ventimask until at least 6 h from induction of anaesthesia.

At 3 h after the first dose of buprenorphine a further 0.3-mg dose was given; group V received this dose i.v. diluted to 10 ml and given over 1 min. Group M received 0.3 mg in 1 ml given by the nursing staff into the vastus lateralis muscle of the side opposite to hip operation. The second dose of buprenorphine was not given unless the patient was able to open the eyes to command. Six hours after the first dose of buprenorphine the patients were connected via a separate i.v. line (21-gauge Butterfly), to a demand analgesia system, the use of which had been explained to them on the previous day. The demand analgesia apparatus was constructed in the Nuffield Department of Anaesthetics from a modified Mill Hill infusion pump (Muirhead Ltd, 34 Croydon Road, Beckenham, Kent), delivering diamorphine 0.25 mg when the patient pressed a button. This was the only postoperative analgesic until the patient left the recovery room on the following morning. The demands for analgesia were recorded automatically over this period.

Arterial pH, $P\text{CO}_2$ and $P\text{O}_2$ were measured during operation, at 150 min after the first dose of buprenorphine and at 10, 60, 120 and 180 min after the second dose, using a Radiometer ABL2 blood-gas analysis system. Plasma cortisol concentration was measured by the method of Murphy (1976), modified by the use of Sephadex instead of Florisil; plasma prolactin concentration was measured using a kit obtained from CIS (U.K.) Ltd, and plasma glucose concentration by a standard glucose oxidase procedure. The samples were taken at the same times as blood was withdrawn for blood-gas analysis, with an additional sample before operation. Plasma buprenorphine concentrations were measured by the method of Bartlett and colleagues (1980), using a phosphate buffer. The kinetic analysis of the data appears elsewhere (Bullingham et al., 1980).

RESULTS

The patient data for the two groups are shown in table I. The age, weight, sex distribution, duration of surgery and Pa_{CO_2} values during operation did not differ significantly for the two groups. The difference in blood loss was matched by transfusion. Anaesthesia was uneventful, with no unexpected changes in heart rate and arterial pressure.

TABLE I. *Patient data for the two groups (mean ± SEM)*

	Group V	Group M
Age (yr)	67.2±2	62.7±2.9
Weight (kg)	68.5±3.7	64.7±3.4
Duration of surgery (min)	95.3±10.1	84.5±5.5
Pa_{CO_2} during operation (kPa)	5.35±0.16	5.47±0.31
Blood loss (ml)	539±94	363±55
Sex distribution	6M : 4F	6M : 4F

After operation the patients were generally well, but one patient in group V was confused and hallucinating for 30 min, following administration of the second dose of buprenorphine (conversation with a non-existent person). Two patients in group V vomited once after the second dose was given and received metoclopramide 10 mg i.m. One patient in group M was nauseated following the second dose, but this resolved spontaneously.

Drowsiness was apparent in all the patients, such that they were clearly distinguishable from other patients in the recovery room who had received fentanyl-based anaesthetics. The patients slept for the first 2–3 h after operation, but were easily roused, and the drowsiness appeared to have no adverse effect. One patient in each group required an oropharyngeal airway for the first 30 min after anaesthesia. These patients then woke uneventfully and received their second dose of buprenorphine.

Analgesia

A continuous record of demands against time was obtained for each patient. The minimum record was for a period of 11.5 h, the maximum 18.6 h. A wide range of demand was observed; one patient in group V making no demands and another in group V making 88 demands (equivalent to diamorphine 22 mg). Such variability required the use of two methods of analysis. Analysis by averaging the data meant that the wealth of information obtained in the record of one patient, effectively a binary 2-min record over a period of at least 10 h, would not be put to best use. Thus the individual patient's data were used in the estimation of duration of action. Mean data were used to compute the respective demands per patient per min for groups V and M.

The automatic recordings of each patient's analgesic demands were analysed for the duration of action of buprenorphine.

Time to the fifth demand made by each patient was used to obtain the estimate of duration. The median value for all the patients was 480 min after the second dose was given.

A number of other criteria of duration of action including time to two, three and four demands and regression to zero demand axis at the time when demands became frequent were used also. These analyses gave median duration values which were very similar to the value obtained by analysis to fifth demand.

Using non-parametric methods, no significant difference was found in the duration of action for the two groups. There was no correlation (Spearman rank test) between the percentage absorption from i.m. administration and the duration of action. There was no correlation between the peak plasma buprenorphine concentration and duration, in either group.

Route of administration and sex difference. The difference in efficacy of buprenorphine i.v. and i.m. was shown by a comparison of the regression slopes obtained from plots of the averaged cumulative demands for each 15-min period against time. The demands made between 60 and 600 min were used for the analysis. Values between 0 and 60 min were excluded because the slopes in the 1st hour were markedly different from the succeeding 10 h.

Subdivision of the groups by sex allowed comparison of the demand rate shown in table II to be made between the men and women of groups V and M. The slope ratios shown in table III allow quantification of the relative effects of sex and route. In section 1 of table III, there is a 1.8–3.3-fold difference in the demand rate, the larger difference being in the i.m. group. In section 2, there is a 1.3–2.4-fold difference, the larger difference being in the females.

TABLE II *Analgesic demand analysis by group and by sex (mean ± SEM). Analgesic demand analysis for 60–600 min of connection to the demand system All the values were significantly different (minimum P value <0.01, maximum $P<0.001$, d.f. = 35) from all other values by comparison of the regression slopes*

	Demand rate (diamorphine mg × 10^{-3} per patient per min)		
	Males	Females	Total
Group V	8.6 ± 0.2	4.8 ± 0.2	7.0 ± 0.3
Group M	6.5 ± 0.2	2.0 ± 0.1	4.7 ± 0.1
Mean	7.6 ± 0.2	3.4 ± 0.2	

TABLE III. *Slope ratios analysed by group and by sex*

Group	Male/female slope ratio
V	1.78
M	3.25
Mean	2.24
Sex	**Group V/group M slope ratio**
Male	1.32
Female	2.41
Total	1.48

Blood-gas analysis results

Table IV shows blood-gas results at 30 min (during operation), 150 min (30 min before the second dose); 10 min and 1, 2 and 3 h after the second dose. Pa_{CO_2} values were increased after operation, but there were no significant differences either between the two groups or between men and

TABLE IV. *Blood-gas analysis results. Combined groups V and M (kPa, mean ± SEM). Sample times are calculated from the time the first dose of buprenorphine was given.* $F\mathrm{I}_{\mathrm{O}_2}$ *= 0.28, but 0.33 at 30-min sample time*

	Sample time (min)					
	30	150	190	240	300	360
Pa_{CO_2}	5.45±0.21	6.65±0.03	6.81±0.26	6.98±0.31	6.84±0.26	6.58±0.24
Range	(3.4–6.5)	(4.6–9.7)	(4.5–8.0)	(4.9–8.9)	(5.6–8.9)	(5.2–8.7)
Pa_{O_2}	19.85±0.85	14.69±1.01	14.25±0.89	14.36±0.90	14.23±0.80	14.26±0.74
$(P\mathrm{A}_{\mathrm{O}_2}-Pa_{\mathrm{O}_2})$	6.9±0.91	6.25±1.16	5.51±0.94	5.54±0.85	5.89±0.98	5.94±0.94

women. Using a paired *t* test, no significant increases in Pa_{CO_2} were found following the second dose of buprenorphine, either at 10 min or 1, 2 or 3 h after the second dose. $(P\mathrm{A}_{\mathrm{O}_2}-Pa_{\mathrm{O}_2})$ was calculated for all patients (Nunn, 1977). The mean difference was greater during, compared with after operation. Shunt values estimated from these mean values remained within the normal physiological range of 3–5%.

Hormones and blood glucose

Plasma glucose concentrations increased during the operation in both groups (fig. 1). Thereafter the concentrations did not change in group V, whilst group M patients showed a continuous decrease in plasma concentrations following the second dose of buprenorphine, with a mean decrease of 1.5 mmol litre^{-1} over the 3-h period ($P<0.01$, paired *t* test).

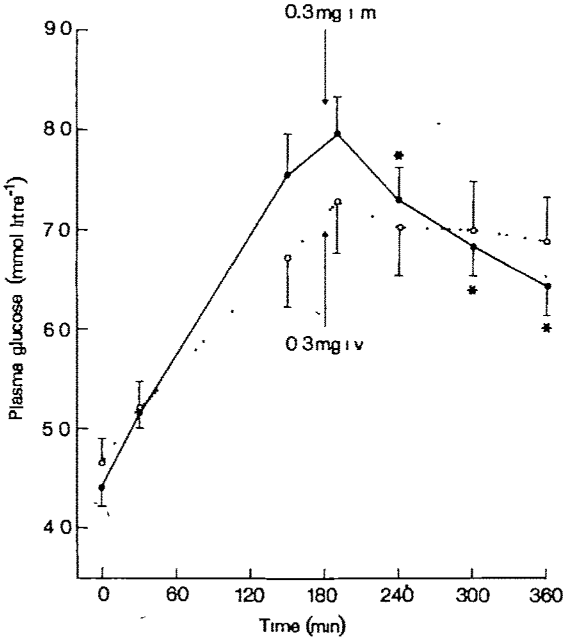

FIG. 1. Plasma glucose concentrations before, during and after operation. Second dose of buprenorphine given at time indicated by arrows. $^{*}P<0.01$.

The increase in plasma cortisol concentrations during surgery was similar in both groups of patients (fig. 2). In group V plasma cortisol concentrations increased by a mean of 272 nmol litre^{-1} ($P<0.01$, paired *t* test) in the 3 h following the second dose. In group M, however, there was a mean decrease of 220 nmol litre^{-1} ($P<0.01$, paired *t* test) in the 1st hour following i.m. administration of the drug. Although the concentrations increased subsequently, they did not differ significantly at the end of the study period from those observed immediately after operation.

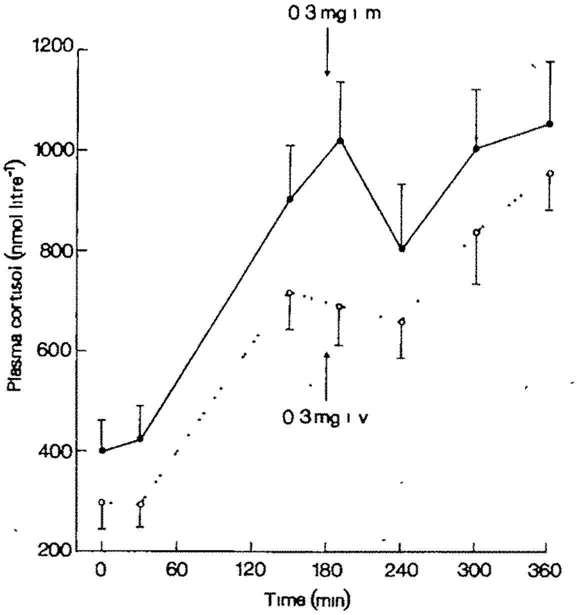

FIG. 2. Plasma cortisol concentrations before, during and after operation. Second dose of buprenorphine given at time indicated by arrows.

TABLE V. *Plasma prolactin concentrations* (*mu. litre*$^{-1}$) (*mean* ± *SEM*)

Time (min)	Group V	Group M
0	279 ± 45	344 ± 61
30	1896 ± 468	1598 ± 162
150	2074 ± 398	2248 ± 353
190	1652 ± 344	1649 ± 286
240	1230 ± 233	1242 ± 157
300	932 ± 165	956 ± 108
360	722 ± 183	785 ± 132

The changes in plasma prolactin concentration which accompany surgery were the same in both groups (table V). There was a seven-fold increase in concentration following operation. There was no significant difference between the groups at any time.

DISCUSSION

The evidence presented here supports the clinical profile of buprenorphine suggested by previous trials. Because this was primarily a kinetic study, the drug was administered twice and the effects might be expected to be greater than for a single administration.

Analgesia

The median duration of analgesia of 480 min resulted from the second dose of buprenorphine 0.3 mg. This is in accordance with single-dose studies which have shown a long duration using other methods of analgesia assessment (Kay, 1978). The explanation of this long duration compared with other opiates is not found in an increase in plasma buprenorphine concentrations, which decrease to very small values by 1 h after the dose is given (Bullingham et al., 1980). The kinetics are similar to those seen with fentanyl (McQuay et al., 1979), which does not give prolonged analgesia.

The slow dissociation constant of the buprenorphine drug–receptor complex (Hambrook and Rance, 1976) provides an explanation because, uniquely among opioid drugs, receptor occupancy will remain high for a long time. This distinction between pharmacokinetic and pharmacodynamic aspects, in which an effect continues at plasma concentrations where none would be anticipated is also seen with non-depolarizing neuromuscular blockers, and a slow drug–receptor dissociation constant is the explanation in that case (Feldman and Tyrell, 1970).

The smaller postoperative analgesic requirement of patients given the second dose of buprenorphine i.m. compared with i.v. was an unexpected finding. The bioavailability of this drug given i.m. is close to 100% (Bullingham et al., 1980), but this finding alone would suggest that there would be no difference between the two routes. For this drug the clue to the relative advantage of the i.m. route may lie in the kinetic analysis. The plasma concentrations following the same dose given by the two different routes show no significant difference after 10 min. Following administration i.v. a greater mass of the drug, initially in the plasma, will be removed by the liver in the first 10 min.

Thus administration i.m. results in the removal of less mass of drug in the initial 10 min, because less drug is in the plasma. Therefore, at 10 min, although the plasma concentrations in the two groups were the same, a greater mass of drug remained in the body in the i.m. case. This extra drug, stored in the tissues, subsequently returns to the plasma, and is available to be associated to the receptor. The receptor affinity of buprenorphine allows pharmacologically effective occupancy of the receptor at small plasma concentrations.

This is supported by current work on comparable patients using sublingual buprenorphine, which has provided excellent analgesia despite plasma concentrations which never exceeded 1 ng ml^{-1} (unpublished observations). The extra drug resulting from i.m. administration caused no measurable change in plasma concentration, but exerted a pharmacological effect in terms of analgesic consumption.

The finding of a smaller analgesic requrement after operation in females substantiates the commonly held view that women need less postoperative analgesia than men, a view which has no support in the literature. The fact that there were no significant differences in the plasma concentrations of the drug between men and women suggests that the explanation lies in an intrinsic difference in the response to pain between men and women, rather than in a specific effect of the drug. This explanation is supported by work with methadone, which resulted in lower pain scores and higher pain relief scores in females compared with males, despite similar plasma concentrations in the two groups (A. B. Kaiko, personal communication). Furthermore, when the pain relief scores for men and women were the same, the plasma concentrations in the female group were less than in the male group. The difference between the sexes found with methadone was seen using classical pain scoring methods, and provides strong support for the difference using demand system analysis in the present study.

This difference is of importance in the testing of analgesics, because data on duration and efficacy obtained in single-sex studies, for example using the episiotomy pain model, may not be comparable with results from studies on both sexes.

Blood-gas analysis

Pa_{CO_2} values were increased after operation. This was not surprising in view of the relatively elderly population studied, the fact that two doses of buprenorphine were used, and the use of diazepam for premedication with halothane as an anaesthetic supplement. There was no significant difference in the Pa_{CO_2} values obtained in this study from those which result from single doses of fentanyl used in a similar group of patients and without the addition of halothane (unpublished observations). This does not support the specific interaction suggested with halothane in the manufacturer's report on the monitored release of buprenorphine, a suggestion which was based solely on measurements of respiratory rate.

That Pa_{CO_2} does not increase following the second dose of buprenorphine is seen when the values at 150 min and at 190 and 240 min are compared. This shows that a proportionate increase dose not follow the second dose, and is evidence in man for a flat dose–response curve (Martin, 1979) which is of clinical importance if the increase in Pa_{CO_2} is limited. One patient, however, who had a history of heavy tobacco smoking, had Pa_{CO_2} values of 9 kPa after operation. No further increase was seen after the second dose, again suggesting that the drug has a flat dose–response curve, operating to the benefit of the patient in this instance of presumed respiratory disease.

Hormones and blood glucose

Group V patients showed changes in plasma concentrations of glucose and cortisol both during and after surgery which were typical of the changes seen in many other studies (Brandt et al., 1976, 1978; Hall et al., 1978; Cooper et al., 1979; McQuay et al., 1979). The substantial effect of i.m. buprenorphine on both cortisol and glucose concentrations was unexpected. Only high doses of fentanyl (Hall et al., 1978) or morphine (George et al., 1974) and extradural blockade (Brandt et al., 1978; Cooper et al., 1979), have been shown previously to obtund the stress response during and after surgery. Although the abrupt decrease in plasma cortisol concentrations was followed by an increase, there was no overall increase after operation in group M compared with group V and compared with the use of fentanyl (McQuay et al., 1979).

The decrease in plasma glucose concentrations was substantial, with a mean decrease of 1.5 mmol litre^{-1} in the 3 h following buprenorphine i.m. The downward trend continued (fig. 1), and it is possible that the prolonged hyperglycaemia which occurs for up to 24 h following operation (Brandt et al., 1978) may be prevented by this route of administration.

There is no obvious explanation for this unique effect of therapeutic doses of i.m. buprenorphine but, just as with analgesic efficacy, i.m. buprenorphine had greater effect than the i.v. dose in reducing the stress response.

The changes in plasma prolactin concentration were of the same magnitude and duration as those shown by Brandt and colleagues (1976), and there was no difference in the rate of decrease of prolactin between the two routes of administration. Buprenorphine differs from the more commonly studied fentanyl and morphine in that it is a mixed agonist–antagonist rather than a pure agonist. There is growing interest in the specific neuro–endocrine effects of opiate drugs (Labrie et al., 1978), and such effects with buprenorphine cannot be excluded.

Buprenorphine, as used in this trial, clearly has little effect on the direct endocrine and metabolic response to surgery. The particular action of i.m. buprenorphine may have important implications for control of the long-term metabolic response to surgery (Brandt et al., 1978; Foster et al., 1979) and deserves investigation in this area.

We believe that buprenorphine has unique properties which, to obtain maximal benefit for the patient, may require that the route and times of administration take account of these properties. The potential benefit to patients suffering from pain after operation is such that further studies are indicated.

ACKNOWLEDGEMENTS

We thank the surgeons of the Nuffield Orthopaedic Centre for allowing us to study their patients, the nursing staff for their help and the staff of the Nuffield Department of Clinical Biochemistry for their technical assistance.

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EFFETS CLINIQUES DE LA BUPRENORPHINE AVANT ET APRES L'INTERVENTION CHIRURGICALE

RESUME

On a fait une étude sur les effets analgésiques, respiratoires et hormonaux qu'ont produits deux doses de buprénorphine, avant et après l'intervention chirurgicale effectuée sur 20 patients subissant un remplacement total de la hanche. Ce médicament a entraîné une analgésie de longue durée. Les effets analgésiques et hormonaux de ce médicament ont été davantage marqués après son administration par voie intramusculaire, qu'après l'administration par voie intraveineuse. Les besoins analgésiques postopératoires des femmes ont été moindres que ceux des hommes. Les différences pharmacodynamiques que l'on a constatées entre les sexes et entre les deux modes d'administration font l'objet d'un exposé comparatif avec la pharmacocinétique du médicament.

KLINISCHE WIRKUNGEN VON BUPRENORPHIN WÄHREND UND NACH DER OPERATION

ZUSAMMENFASSUNG

Die schmerzlindernden, respiratorischen und hormonalen Wirkungen von zwei Dosen Buprenorphin wurden wahrend und nach Hüftersatz-Operationen an 20 Patienten studiert. Die Droge hatte eine langandauernde schmerzlindernde Wirkung, und sowohl diese wie auch die hormonale Wirkung waren nach intramuskulärer Verabreichung starker als nach intravenöser Verabreichung. Die Erfordernisse für Schmerzlinderung nach der Operation waren bei Frauen geringer als bei Männern. Diskutiert werden die sich ergebenden pharmakodynamischen Unterschiede zwischen den Geschlechtern und zwischen den beiden verschiedenen Verabreichungsarten, im Bezug auf die pharmakokinetischen Eigenschaften der Droge.

EFECTOS CLINICOS DE LA BUPRENORFINA DURANTE LA OPERACION Y DESPUES DE ESTA

SUMARIO

Durante la operación y después de ésta, se estudiaron los efectos analgésicos, respiratorios y hormonales de dos dosis de buprenofina, en 20 pacientés sometidos a sustitución total de la cadera. La droga proveyó analgesia de larga duración. Los efectos analgésicos y hormonales de la droga fueron superiores después de la administración intramuscular, en vez de después de la administración intravenosa. El analgésico posoperativo necesario para las mujeres fue inferior al de los hombres. Las diferencias farmacodinámicas entre los sexos y entre las dos rutas de administración se discuten en relación a las farmacocinéticas de la droga.

Br. J. Anaesth. (1980), 52, 1021

INFUSION MODEL FOR FENTANYL BASED ON PHARMACOKINETIC ANALYSIS

J. H. HENGSTMANN, H. STOECKEL AND J. SCHÜTTLER

SUMMARY

The calculation of pharmacokinetic parameters after a bolus injection of fentanyl allowed an i v infusion scheme which guarantees analgesia for the entire duration of surgery, with the advantage of steady plasma concentration and body content. In the initial phase after bolus injection, the serum concentration decreased rapidly for about 10 min, indicating extensive transfer to the peripheral compartment This was followed by a slower elimination phase with a half-life of about 2 h. The total volume of distribution of 80 litre exceeded the body weight only slightly. The total plasma clearance was 500 ml min^{-1}. In developing a model for total i.v. anaesthesia we considered two different consecutive infusion rates. The pharmacokinetic model proved to be valid for all patients. The plasma concentrations during anaesthesia coincided well with the predicted steady state plasma concentrations and provided continuous analgesia during operation.

Inhalation anaesthesia uses the model of continuous drug delivery as a well established and practical method for adequate and efficient hypnosis and analgesia. Dosage regimens for i.v. anaesthetics are usually used according to the personal skill and experience of the anaesthetist. Nowadays, repetitive dosing is the usual regimen for balanced i.v. anaesthesia. For the inexperienced anaesthetist there are anxieties about periods when analgesia is less than desired or the total body content of drug is unnecessarily large. For practical purposes a standardization of dose intervals is not possible so that signs of reflex autonomic responses such as tachycardia, arterial pressure increase, lacrimation and sweating are commonly the criteria for the next injection.

The constant infusion of i.v. anaesthetics is thought to be advantageous for a smooth and adequate depth of anaesthetic. Generally, three or four biological half-lives must pass in the case of a constant rate infusion before steady state conditions are attained. One way of reaching therapeutic concentrations rapidly is an initial bolus injection. Depending on the pharmacokinetic properties of a drug, problems may arise, however, during the early period of anaesthesia and surgery when the effects of the bolus injection have decreased and a steady state from the infusion is not established yet.

For drugs with these special problems, Wagner (1974) has described a model based on two different consecutive i.v. infusion rates. Initial excessive plasma concentrations are prevented and therapeutic plasma plateaux are achieved rapidly and safely with only a minor time lag.

METHODS

Fentanyl was available as the citrate salt in 10-ml vials. Doses and concentrations given refer to the free base. Concentrations of fentanyl in plasma were determined by radioimmunoassay (Michiels, Hendriks and Heykants, 1977). The coefficient of variation was ±5% for a concentration of 1 ng ml^{-1} (0.97 ± 0.05 ng ml^{-1}) and ±10.2% for a 5-ng ml^{-1} sample.

All the patients studied gave informed consent to the investigation. In five patients (age 32.2 ± 6.1 yr, body weight 62.2 ± 9.1 kg) a bolus dose of fentanyl 0.5 mg was given into a forearm vein immediately after tracheal intubation. Venous blood was sampled from another forearm vein through a plastic cannula at 2, 5, 7, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180 and 240 min after injection.

Six patients (age 46.3 ± 5.9 yr, body weight 63 ± 9.5 kg) undergoing abdominal hysterectomy were premedicated with promethazine 50 mg and atropine 0.5 mg, both given 1 h before operation. Anaesthesia was induced with etomidate 20 mg.

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0007–0912/80/101021–05 $01.00

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Suxamethonium 1.5 mg kg^{-1} was given before tracheal intubation.

Following bolus injection of fentanyl 0.5 mg, plasma concentrations were processed by regression analysis resulting in the hybrid constants A, B, α and β. Calculation of the pharmacokinetic parameters was as described by Riegelman and Loo (1968). The average results of the five patients were taken for further estimation. Total plasma clearance was calculated by dividing the injected dose by the area under the plasma concentration curve from time zero to infinity. The volume of distribution (V^{β}) was determined as the quotient of total plasma clearance and the hybrid constant β.

According to the pharmacokinetic results of the bolus injection study, dose and duration of the infusion rates for the infusion model had to be calculated as described by Wagner (1974). Given an effective fentanyl plasma concentration of 20–25 ng ml^{-1} (Stoeckel et al., 1979) and a total plasma clearance of 450 ml min^{-1} the maintenance infusion rate had to be set to 9 μg min^{-1}. Depending on a biological half-life of 1.5 h, and 5 min chosen for the duration of the fast initial infusion, the ratio of the infusion rates had to be read from the diagram (Wagner, 1974) and multiplied by the maintenance infusion rate, which resulted in a value of 250 μg min^{-1}.

Hence, after tracheal intubation, fentanyl was infused at 250 μg min^{-1} over 5 min for induction and at 9 μg min^{-1} for maintenance of anaesthesia in combination with 60% nitrous oxide in oxygen. Myoneural blockade was maintained with pancuronium bromide (total dose 6–8 mg). The lungs were ventilated artificially with a semi-closed system (Spiromat 650, Dräger).

Blood was sampled at 2, 4, 6, 10, 15, 20, 30, 40, 60, 80, 100, 120, 130, 150, 180, 210 and 240 min after starting the infusion.

RESULTS

Following a bolus injection of fentanyl 0.5 mg plasma concentrations decreased within 10 min from 50 ng ml^{-1} to 5 ng ml^{-1} (fig. 1). The second slope had a half-life of about 2 h. The average volume of distribution was 80 litre and total plasma clearance approximately 500 ml min^{-1}. The biological half-life averaged 140 ± 60 min (table I).

In the six patients who received a continuous infusion the desired therapeutic concentration was exceeded 2–4 min after the start of the fast infusion

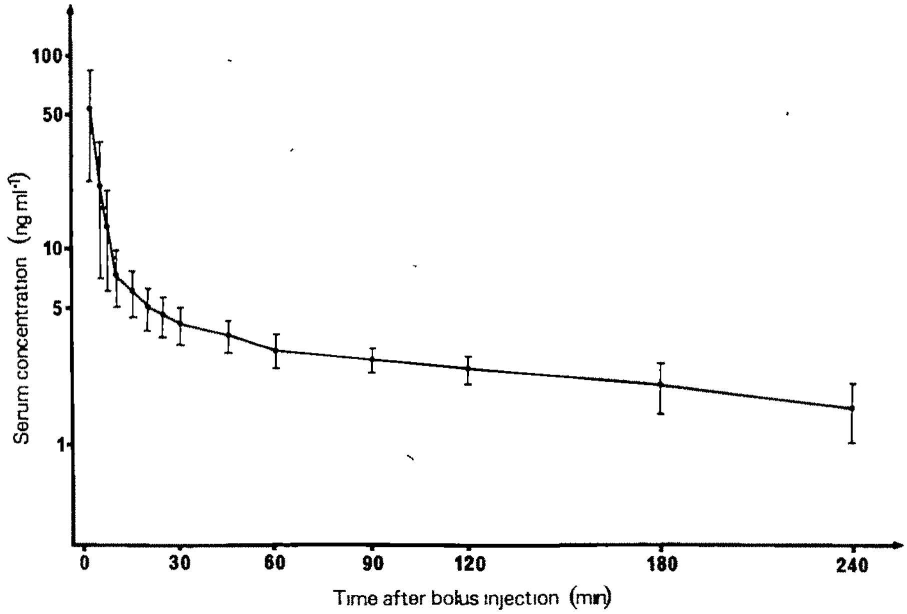

FIG. 1. Serum concentrations in five patients following a bolus injection of fentanyl 0.5 mg. Mean and standard deviation.

TABLE I. *Pharmacokinetic parameters for the two-compartment open model in five patients following a bolus injection of fentanyl 0 5 mg*

	Sex	Age (yr)	Wt (kg)	A (ng ml^{-1})	B (ng ml^{-1})	α	β	k_{12}	k_{21}	k_{10}	V_1 (litre)	$V_{d\beta}$ (litre)	Cl^{tot} (ml min^{-1})	$T_{\frac{1}{2}}^{\beta}$ (min)
A. T.	F	37	62	127.7	5.1	0.752	0.006	0.59	0.03	0.13	3.8	82	490	116
E. W.	F	38	67	58.4	6.9	0.614	0.008	0.47	0.07	0.07	7.4	64	547	87
M. K.	F	23	47	163.4	5.8	0.543	0.004	0.42	0.02	0.10	3.0	71	311	173
E. K.	F	33	65	176.8	3.2	0.359	0.003	0.22	0.01	0.12	2.7	102	347	231
R. D.	F	30	70	88.6	4.8	0.228	0.007	0.13	0.02	0.08	5.3	67	447	99
Mean		32.2	62.2	123.0	5.2	0.499	0.006	0.37	0.03	0.10	4.4	77	428	141
SD		6.1	9.1	50.0	1 4	0.207	0.002	0.19	0.02	0.02	2.0	15	98	60

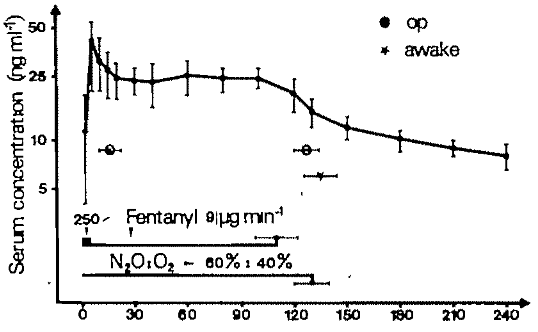

FIG. 2. Serum concentrations in six patients during and following fentanyl infusion. Mean and standard deviation.

(fig. 2). The greatest measured plasma concentrations were at 6 min. Thereafter, plasma concentrations decreased within 10 min to the desired range of 20 ng ml^{-1} with narrow inter-individual variations (table II). The maintenance infusion could be stopped 15 min before the end of the operation (table III). The patients were awake 10 min later when nitrous oxide in the ventilating gas was replaced by oxygen.

DISCUSSION

There are two aims to be satisfied by an infusion model. First, therapeutic concentrations have to be reached as early as possible and, second, any

TABLE II. *Serum concentrations (ng ml^{-1}) in six patients during and after fentanyl infusion (mean ± SD)*

	Time (min)																
	2	4	6	10	15	20	30	40	60	80	100	120	130	150	180	210	240
Mean	12.7	32.7	43.5	29.2	26.2	22.5	22.2	22.8	25.3	24.2	24.5	19.5	14.8	11.7	11 7	9.8	8.3
SD	10.1	21.8	26.8	13.5	7.4	7.5	4.5	7.0	5.8	4.5	3.6	4.7	3.9	2.3	3 0	2 8	2.2

TABLE III. *Age, body measurements and clinical data in six patients undergoing fentanyl infusion and nitrous oxide anaesthesia. Individual values (mean ± SD)*

Patient	Age (yr)	Wt (kg)	Ht (cm)	Duration of infusion (min)	Duration of surgery (min)	Awake after (min)	Total dose (mg)
K. S.	47	70	155	105	120	140	2.15
M. M.	42	57	172	125	150	155	2 33
T. M.	57	61	165	100	120	125	2 11
I. M.	46	79	164	95	100	110	2 06
I. W.	46	56	160	120	135	145	2.29
S. L.	40	55	164	120	130	135	2.29
Mean	46.3	63.0	163.3	110.8	125.8	135.0	2.21
SD	5.9	9.5	5.7	12.4	16.9	15.8	0 11

major deviation from the therapeutic concentration during the course of surgery should be prevented. This is most important for longer surgical procedures. Without pharmacokinetic analysis unwanted accumulation of drug may occur. On the other hand, empirically established dosage regimens have the disadvantage of decreasing efficacy because the amount of drug in the body may become too small. All these disadvantages may be overcome by continuous infusion with constant plasma concentrations.

Theoretically therapeutic plasma concentration plateaux can be attained by one or several bolus injections, by a loading dose followed by a continuous infusion, and by two different consecutive infusion rates (Wagner, 1974). For the "Wagner scheme" some pharmacokinetic parameters have to be established from plasma data following a bolus injection. However, secondary increases in plasma concentrations were observed in some patients (Stoeckel, Hengstmann and Schüttler, 1979). Therefore, we omitted the concentration values during this phase and calculated our parameters according to an open two-compartment model.

The problem of the optimum effective steady state plasma concentration was solved by comparison with spectral analysis of the e.e.g. (Stoeckel et al., 1979). For our anaesthetic model using a combination of fentanyl with 60% nitrous oxide in oxygen, myoneural block and artificial ventilation without any additional drugs, concentrations of 20–25 ng ml^{-1} of fentanyl in plasma were found to be optimal concentrations for operations with a pain level comparable to gynaecological laparotomy in patients with normal circulatory function, body-weight of about 65 ± 15 kg and non-geriatric age. This target concentration is, however, only necessary for the anaesthetic model described. If other drugs such as those commonly used in neuroleptanaesthesia are added, smaller target concentrations are required.

Because adequate analgesia in our model depended on significantly greater plasma fentanyl concentrations compared with those used in neuroleptanaesthesia, the plasma concentrations at the end of surgery were such that the needs of postoperative care must be demanding, and adequate antagonism by naloxone is necessary and continuing artificial ventilation may be required.

The fentanyl infusion scheme can also be used in combination with other anaesthetic drugs, thereby enabling nitrous oxide to be replaced by i.v. hypnotics or benzodiazepines. If nitrous oxide as used in the present model is replaced by other drugs, it is necessary to change the infusion rate of fentanyl by a factor which can be found out by comparison of the modified steady state plasma concentrations with pharmacodynamic parameters indicating the depth of anaesthesia. In a modified model, the principle of the described infusion scheme will be left unchanged; only the amounts of fentanyl in the initial and maintenance infusion periods have to be adjusted.

ACKNOWLEDGEMENTS

We are grateful to Drs Michiels and Heykants, Janssen Pharmaceutica, Research Laboratoria, Beerse/Belgium for the gift of ^{3}H-fentanyl and fentanyl antibodies.

This work was supported by a grant from Ministerium für Wissenschaft und Forschung, NRW, Germany (06/0604/68511).

J H. H. was supported by Deutsche Forschungsgemeinschaft (He 791).

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MODELE DE PERFUSION POUR LE FENTANYL BASE SUR UNE ANALYSE PHARMACOCINETIQUE

RESUME

Le calcul des paramètres pharmacocinétiques après l'injection d'un bol de fentanyl a permis de faire un projet de perfusion intraveineuse qui garantit l'analgésie pendant toute la durée de l'intervention chirurgicale, tout en présentant les avantages d'une concentration régulière dans le plasma et dans la teneur en corpuscules. Dans la phase initiale qui suit l'injection du bol, la concentration dans le sérum a diminué rapidement pendant environ 10 mn, ce qui a indiqué qu'il se produisait un transfert très important au compartiment périphérique. Ceci a été suivi d'une phase d'élimination plus lente avec une demi-vie d'environ 2 h. Le volume total de répartition de 80 litre n'a dépassé que très légèrement le poids du corps. Le coefficient

total d'épuration du plasma a été de 500 ml mn^{-1}. En mettant au point un modèle pour une anesthésie totale par voie intraveineuse nous avons tenu compte des deux taux consécutifs de perfusion différents. Il a été prouvé que le molèle pharmacocinétique est valable pour tous les patients. Les concentrations qui se produisent dans le plasma pendant l'anesthésie coïncident bien avec l'équilibre cinétique prévu pour les concentrations dans le plasma et ont assuré une anesthésie continue pendant l'intervention chirurgicale.

AUF PHARMAKOKINETISCHER ANALYSE BASIERENDES INFUSIONSMODELL FÜR FENTANYL

ZUSAMMENFASSUNG

Die Errechnung von pharmakokinetischen Parametern nach einer Fentanyl-Bolusinjektion erlaubte die Ausarbeitung eines intravenösen Infusionsschemas, welches einerseits eine adaequate Analgesietiefe für die gesamte Operationsdauer garantierte und andererseits sowohl konstante Plasmaspiegel als auch einen gleichbleibleibenden Körperbestand von Fentanyl gewährleistete. Nach Bolusinjektion von Fentanyl 0,5 mg zeigt sich ein schnelles initiales Absinken der Plasmaspiegel über einen Zeitraum von 10 Minuten. Dieser wird von einer zweiten langsamen Eliminationsphase gefolgt, die eine Halbwertzeit von ca. 2 Stunden aufweist. Das Gesamtverteilungsvolumen übersteigt mit 80 Litern nur gering das Körpergewicht. Die totale Plasmaclearance erreicht einen Wert von fast 500 ml min^{-1}. Bei der Entwicklung eines Modells für die totale intravenöse Anästhesie entschieden wir uns für ein Infusionsschema mit zwei unterschiedlichen aufeinanderfolgenden Infusionsraten. Das pharmakokinetisch begründete Modell zeigte bei allen Patienten annähernd die vorausberechneten Plasmaspiegel und gewährleistete eine adaequate Narkosetiefe über die gesamte Operationsdauer.

MODELO DE INFUSION PARA FENTANIL, BASADO EN EL ANALISIS FARMACOCINETICO

SUMARIO

El cálculo de los parámetros farmacocinéticos, después de la inyección de un bolo de fentanil, permitió llevar a cabo un programa de infusión intravenosa que garantizó analgesia durante la duración total de la operación, con la ventaja de presentar una concentración constante de plasma y un contenido constante de cuerpos. En la fase inicial después de la inyección del bolo, la concentración de suero disminuyó rápidamente por espacio de 10 minutos, indicando la transferencia extensiva al compartimiento periférico. A esto le siguió una fase de eliminación más lenta con una vida media de 2 horas aproximadamente. El volumen total de la distribución de 80 litros, excedió el peso del cuerpo tan sólo de forma ligera La separación total del plasma fue de 500 ml min^{-1}. Al desarrollar un modelo para la anestesia total intravenosa se consideraron dos regímenes de infusión diferentes y consecutivos. El modelo farmacocinético demostró ser válido para todos los pacientes. Las concentraciones de plasma durante la anestesia coincidieron de forma adecuada con las concentraciones predichas de plasma de estado constante y proveyeron una analgesia continua durante la operación.

Br. J. Anaesth. (1980), **52**, 1027

PLASMA CORTISOL CONCENTRATIONS DURING CAESAREAN SECTION

Y. NAMBA, J. B. SMITH, G. S. FOX AND J. R. G. CHALLIS

SUMMARY

The effects of extradural and general anaesthesia on the adrenocortical response to elective or emergency Caesarean section were studied in 72 patients. Maternal plasma concentrations of cortisol were measured before surgery, at delivery, and 30 and 60 min after skin incision. Umbilical vein and artery plasma cortisol concentrations at delivery were determined also. Maternal plasma cortisol concentrations in patients receiving extradural anaesthesia did not change significantly from control at any of the time intervals. In the general anaesthesia group concentrations were significantly increased from control, at 30 and 60 min after skin incision for elective Caesarean sections, and at 60 min after skin incision during emergency surgery. There were no significant differences between the mean umbilical vein and artery plasma cortisol concentrations compared within or between extradural or general anaesthesia groups. Extradural anaesthesia, in contrast to general anaesthesia, decreases the adrenocortical response to Caesarean section surgery by blocking afferent neurogenic pathways from the surgical site. The method of anaesthesia does not influence the fetal cortisol response.

The endocrine and metabolic response to surgery is associated with an increase in the secretion of catabolic hormones, for example cortisol, glucagon and catecholamines. Insulin and testosterone, both anabolic hormones, are inhibited during this response (Thorén, 1974). Recently, during intra-abdominal surgery, extradural anaesthesia, in contrast to general anaesthesia, has been shown to modify or abolish the endocrine changes by blocking afferent neurogenic pathways from the surgical site (Lush et al., 1972; Engquist et al., 1977; Madsen et al., 1977). During labour, the progressive increase in plasma cortisol concentrations in patients receiving parenteral analgesics is minimized by extradural analgesia (Buchan, Milne and Browning, 1973).

At present, no data exist describing the adrenocortical response during Caesarean section with either extradural or general anaesthesia. We measured maternal plasma concentrations of cortisol at intervals during elective and emergency Caesarean section. Umbilical vein and artery cortisol concentrations at delivery were determined also.

PATIENTS AND METHODS

Four groups of patients were studied (table I). For elective surgery, 24 patients received extradural anaesthesia and 25 general anaesthesia, according to their choice. These two groups were comparable in age and weight and no patient was taking any medication or had evidence of systemic disease or complications of pregnancy. Fetal gestational age was 38 weeks or greater and all presentations were cephalic as determined by ultrasonography.

Ten patients undergoing emergency surgery received extradural anaesthesia and 13 general anaesthesia. The indications for emergency surgery were failure of labour to progress satisfactorily or persistent pathological fetal heart rate patterns, or both.

An infusion of physiological salt solution was started through a large-bore i.v. catheter in all four groups of patients on arrival at the operating room. After institution of extradural anaesthesia and during preparation for general anaesthesia, the patients were in the supine position with left lateral tilt (wedge under the right hip). They were maintained in this position until delivery of the baby and clamping of the umbilical cord.

Patients were premedicated with atropine 0.4 mg i.m. and antacid 30 ml orally.

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0007-0912/80/101027-06 $01.00

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Extradural anaesthesia for elective Caesarean section was managed in the manner described previously (Fox et al., 1979). Sixteen to 20 ml of lignocaine hydrochloride 2% with adrenaline 1: 200 000 was injected to produce sensory blockade to T4 or T5. Associated hypotension, not responsive to fluid load and left uterine displacement was treated with ephedrine i.v. 5–10 mg i.v. Extradural anaesthesia in the emergency group was achieved by injection of lignocaine 2% with adrenaline 1: 200 000 through an extradural catheter previously placed for control of pain during labour in three patients, and started *de novo* in seven patients. All patients breathed a high inspired oxygen concentration delivered by facemask for at least 10 min before delivery.

General anaesthesia for both elective and emergency surgery was conducted as follows: Anaesthesia was induced only after the patients were prepared and draped for surgery. The patients were preoxygenated for at least 3 min before induction of anaesthesia. Following tubocurarine 3 mg i.v., a dose of thiopentone 2.5% sufficient to abolish the eyelash reflex was injected. The trachea was intubated after the i.v. injection of suxamethonium. A modified Bain attachment was used and ventilation was controlled to maintain normal maternal carbon dioxide tensions. Anaesthesia was maintained from induction to delivery with nitrous oxide 33% in oxygen, supplemented with halothane 0.5%. Following delivery of the neonate, halothane was discontinued, the nitrous oxide concentration was increased to 66% in oxygen and fentanyl 0.05–0.1 mg i.v. was used to supplement analgesia. An infusion of suxamethonium 0.1% was used throughout surgery to produce adequate neuromuscular blockade.

In all groups, synthetic oxytocin drug 5 u. was injected i.v. after umbilical cord clamping. This was followed by a continuous infusion of oxytocin 10 u. in 500 ml of solution.

Maternal blood samples for measurement of plasma cortisol concentrations were obtained from a vein opposite to that used for the i.v. infusion. Fetal samples were obtained from a doubly clamped segment of umbilical cord. Control venous samples were obtained before induction of general anaesthesia or initiation of extradural blockade. In the patients undergoing emergency surgery with extradural analgesia, the control samples were obtained before augmentation of the block. In all groups further samples were taken at delivery of the baby, and 30 and 60 min after skin incision.

All blood samples were collected in heparinized syringes, centrifuged and the plasma stored at −20 °C until assay. After ethanol 0.5 ml extraction of 0.1 ml of plasma, total plasma cortisol concentrations were measured by radioimmunoassay (Challis et al., 1977). For maternal plasma this assay measured, essentially, unconjugated cortisol. In the fetal circulation, this relationship may not always apply, because of substantial secretion of cortisol sulphate by the fetal adrenal glands (Sharpe-Cageorge et al., 1977) and the probability that maternal unconjugated cortisol contributes after transplancental transfer to the pool of cortisol in the fetal compartment (Challis and Thorburn, 1976). Our measurements of fetal cortisol concentrations are therefore expressed as "total cortisol" and include cortisol sulphate and corticosterone.

The results at each collection interval were expressed as per cent change from control because normal cortisol concentrations exhibit marked circadian fluctuations. Analysis of variance was applied to each group of maternal results. Students' t test for unpaired groups was applied to the fetal results. A P value <0.05 was considered a significant change.

RESULTS

All deliveries occurred between 08.00 and 15.00 h. Pre-anaesthetic absolute values of maternal plasma cortisol are shown in table I.

TABLE I. *Study groups and control plasma concentrations* (*ng* ml^{-1}) *of cortisol (mean values* ± *SEM)*

	Number of patients	Control plasma cortisol concns
General anaesthesia		
Elective	25	314 ± 30
Emergency	13	280 ± 25
Extradural anaesthesia		
Elective	24	289 ± 28
Emergency	10	359 ± 33

Eight patients in the elective extradural group, but none of the remaining patients, required ephedrine i.v. to correct arterial hypotension. The cortisol concentrations in the ephedrine-treated group were similar to those of the other patients within this group, and therefore all results are reported together.

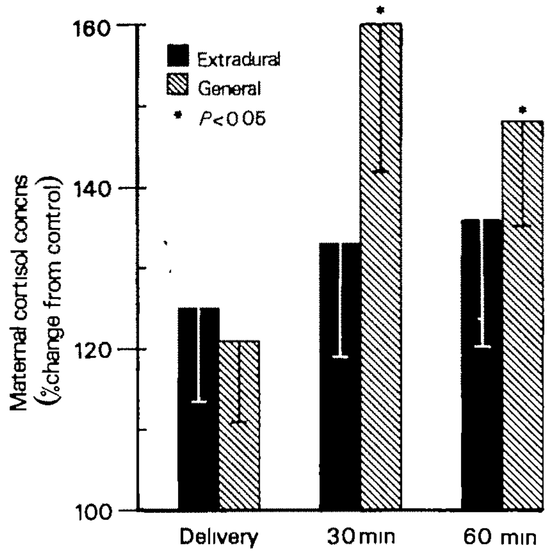

FIG. 1. Percentage change in maternal plasma cortisol concentrations at delivery, 30 and 60 min after skin incision during elective Caesarean section.

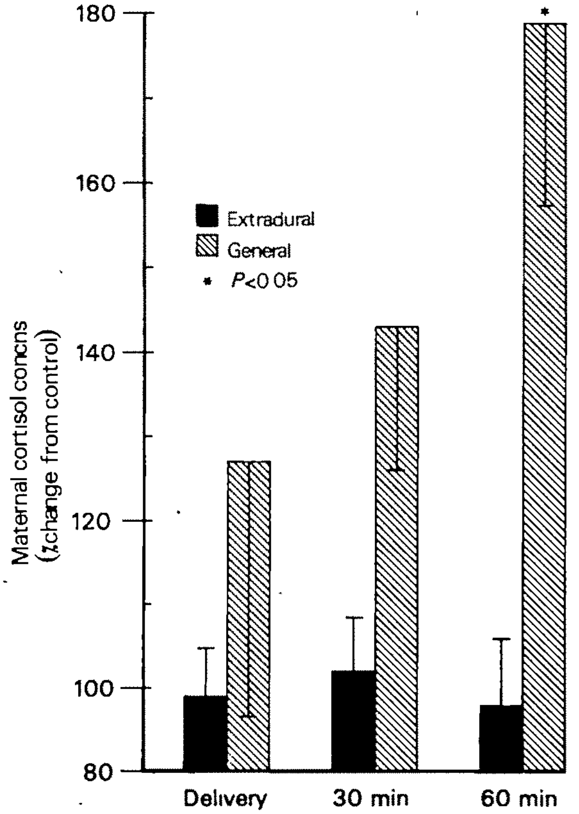

FIG. 2. Percentage change in maternal plasma cortisol concentrations at delivery, 30 and 60 min after skin incision during emergency Caesarean section.

Maternal plasma cortisol concentrations at delivery and 30 and 60 min after incision during elective surgery are shown in figure 1 as a percentage change from control concentrations (±SEM). The general anaesthesia group had an increase to 121%(±10), 160%(±18) and 148%(±12.7) of the pre-anaesthetic concentration at delivery, 30 and 60 min after incision. In the extradural group the increase was to 125%(±11.5), 133%(±13.8) and 136% (±15.7) of control concentrations at delivery, 30 and 60 min after incision. The concentrations 30 and 60 min after incision in the general anaesthesia group were the only values significantly different from concentrations before anaesthesia in both elective groups.

The per cent change in maternal cortisol concentrations during emergency Caesarean section are shown in figure 2. Minor non-significant fluctuations occurred during extradural anaesthesia. These changes were 99% (±5.8), 102% (±6.3) and 97% (±8.8) at delivery, 30 and 60 min after incision. The changes during general anaesthesia were much greater. These were 127% (±30), 143% (±17) and 179% (±21.5) at delivery, 30 and 60 min, with the value 60 min after incision being significantly different from control.

Umbilical vein and artery total cortisol concentrations during elective surgery are shown in table II. There was no difference between the mean venous and arterial concentrations compared with each other or between the extradural or general anaesthesia groups. There was no correlation in either group between maternal and umbilical venous or arterial concentration.

TABLE II. *Umbilical vein (UV) and umbilical artery (UA) plasma concentrations (ng ml^{-1}) of cortisol during elective Caesarean section (mean values ± SEM)*

	Number of samples	UV	UA
General anaesthesia	22	198 ± 19	187 ± 19
Extradural anaesthesia	18	216 ± 22	200 ± 23

Umbilical cortisol concentrations during emergency sections are not shown because too few results were obtained to allow statistical analysis.

DISCUSSION

The normal metabolic response to surgical stress is shown in figure 3. The hypothalamus receives neurally mediated input from the surgical site. In addition, the hypothalamus receives input from the higher centres which may be psychological in origin, for example, fear or anxiety. In response to these stimuli, the hypothalamus releases corticotropin releasing factor (CRF) which induces the anterior pituitary gland to secrete ACTH. The latter hormone directly affects the adrenal cortex to increase cortisol secretion. A second response to hypothalamic stimulation is increased sympathetic nervous system activity. This in turn causes an increase in the release of catecholamine from the adrenal medulla and increase in the secretion of pancreatic glucagon. Extradural analgesia can play a major role in modifying the stress response by blocking noxious afferent stimuli from the surgical site.

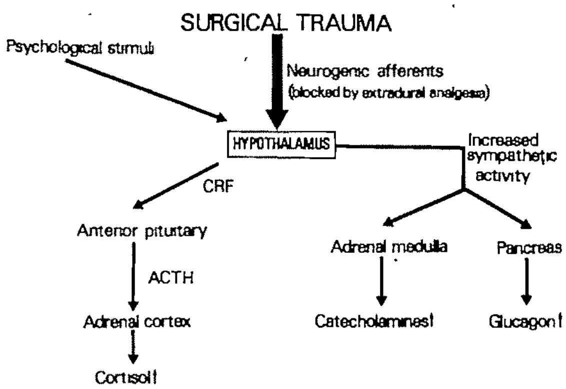

FIG. 3. The metabolic stress response to surgery.

Most reports (Lush et al., 1972; Gordon, Scott and Percy Robb, 1973; Brandt et al., 1976; Madsen et al., 1977) regarding the effects of surgical stress and influence of anaesthesia on the endocrine response are from studies in which extradural anaesthesia has been combined with general anaesthesia. However, Brandt and colleagues (1978) compared the cortisol response to abdominal hysterectomy during general anaesthesia or extradural anaesthesia alone. During general anaesthesia an increase occurred in plasma cortisol concentration which was not seen during extradural anaesthesia.

Chattoraj and his colleagues (1974) reported maternal cortisol concentrations at delivery during Caesarean section following spinal or general anaesthesia. He did not apply statistical analysis to his results, but the mean concentrations of cortisol were greater during general anaesthesia. Buchan, Milne and Browning (1973) demonstrated that maternal cortisol concentrations do not increase when extradural analgesia is given during labour. However, a marked and progressive increase in cortisol concentration is found when narcotic analgesia is utilized for pain relief.

Our present study with Caesarean sections confirms previous reports that extradural analgesia modifies the cortisol response to surgery, while general anaesthesia fails to do so. The percentage changes in maternal cortisol concentrations are remarkably constant at all sampling times within both extradural groups. The small but non-significant increases seen at all time intervals during elective surgery may represent psychological hypothalamic stimulation attributable to surgery in the awake state. During emergency Caesarean section these small increases in cortisol concentration were not seen because stress stimulation was high before control blood sampling, probably because of labour, pain and the decision to perform previously unanticipated surgery. This is substantiated by the greater control cortisol concentrations in the emergency extradural group (table I).

In contrast to extradural anaesthesia, the increases in plasma cortisol concentrations during general anaesthesia achieved statistical significance at 30 and 60 min following skin incision in the elective group and at 60 min in the emergency group. Although an increase in mean plasma cortisol concentration was seen at delivery, the difference from baseline was small because the cortisol response to surgical stimulation takes several minutes to occur. The skin incision to delivery interval ranged from 5 to 9 min and the cortisol response to stress may not be fully developed in all patients at delivery. By 30–60 min the increase in plasma cortisol can be detected easily. This is in agreement with Brandt and coworkers (1978) who also noted significant differences at 30 and 60 min following the start of surgery.

It is unlikely that the change in anaesthetic technique following delivery of the baby influenced the cortisol concentrations because during surgical stimulation, neither thiopentone, halothane, nitrous oxide (Oyama et al., 1971; Oyama,

1973) or narcotics (Oyama and Takiguchi, 1970) prevent the increase in cortisol concentrations.

We did not find a correlation between maternal plasma and cord cortisol concentrations. Nor did we find any significant difference in the umbilical artery and umbilical vein concentrations of cortisol as suggested by some (Leong and Murphy, 1976), but not by other authors (Fencl, Osathanondh and Tulchinsky, 1976). Interpretation of cord cortisol concentrations is difficult, because the steroid may be derived from fetal adrenal secretion or transplacental transfer from the mother (Thorburn and Challis, 1979). However, comparison of umbilical artery concentrations, which are more likely to reflect fetal adrenal production, does not indicate any marked difference in the "stress" response of the neonates to different methods of anaesthesia.

This study demonstrates that extradural analgesia, as compared with general anaesthesia, reduces the maternal cortisol stress response during Caesarean section. However, the technique of anaesthesia does not appear to influence the stress response in the fetus.

ACKNOWLEDGEMENT

This work was supported in part by M R.C. Grant MA-6070

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CONCENTRATIONS DE CORTISOL DANS LE PLASMA PENDANT UNE OPERATION CESARIENNE

RESUME

On a étudié, sur 72 patientes, les effets qu'ont les anesthésies extradurales et générales sur la réaction cortico-surrénale à l'opération césarienne d'urgence ou effectuée à froid. On a mesuré les concentrations de cortisol dans le plasma maternel avant l'opération, au moment de l'accouchement, puis 30 min et 60 min après l'incision de la peau. On a également déterminé les concentrations de cortisol qui se trouvaient dans le plasma de la veine et de l'artère ombilicales au moment de l'accouchement. Les concentrations de cortisol dans le plasma maternel des patientes ayant subi une anesthésie extradurale n'ont à aucun moment varié d'une manière significative par rapport aux valeurs témoins. En ce qui concerne le groupe soumis à une anesthésie générale, les concentrations ont augmenté d'une manière significative par rapport aux valeurs témoins, 30 min et 60 min après l'incision de la peau lors des opérations césariennes effectuées à froid, et 60 min apres l'incision de la peau lors des opérations d'urgence. Il n'y a eu aucune différence notoire entre les concentrations moyennes de cortisol dans le plasma de la veine et de l'artère ombilicales entre les groupes ou parmi les groupes soumis à l'anesthésie générale ou à l'anesthésie extradurale. Contrairement à l'anesthésie générale, l'anesthésie extradurale a fait baisser la réaction cortico-surrénale à l'opération césarienne en bloquant les voies d'accès neurologiques afférentes venant du terrain d'opération. La méthode utilisée pour l'anesthésie n'influence pas la réaction du foetus au cortisol.

PLASMA-CORTISOLKONZENTRATIONEN WÄHREND KAISERSCHNITT

ZUSAMMENFASSUNG

Die Wirkungen extraduraler und allgemeiner Narkose auf die Nebennierenrinden-Reaktion auf geplanten oder notmassigen Kaiserschnitt wurde in 72 Patientinnen studiert, deren Plasma-Cortisolkonzentrationen vor dem Schnitt, bei Geburt und 30 und 60 Minuten nach dem ersten Einschnitt gemessen wurden, ebenso wie solche Konzentrationen in Nabelvene und Nabelarterie bei der Geburt. Die Cortisolkonzentrationen bei Patientinnen, die extradurale Narkose erhielten, anderten sich gegenuber dem Kontrollwert in keinem der Zeitintervalle wesentlich. Bei allgemeiner Narkose stiegen die Konzentrationen 30 und 60 Minuten nach dem ersten Einschnitt bei geplanten Kaiserschnitten stark an, und bei Not-Operationen 60 Minuten nach dem ersten Hauteinschnitt. Zwischen den mittleren Konzentrationen in Nabelvene und Nabelarterie gab es keine wesentlichen Unterschiede zwischen den beiden Narkosegruppen. Extradurale Narkose senkt im Gegensatz zur allgemeinen Narkose die Reaktion der Nebennierenrinde auf Kaiserschnitt, indem afferente neurogene Leitungen von der Operationsstelle her blockiert werden. Die Narkosemethode beeinflusst die fotale Cortisolreaktion nicht.

CONCENTRACIONES DE PLASMA CORTISOL DURANTE LA OPERACION DE CESAREA

SUMARIO

Se estudiaron en 72 pacientes los efectos de la anestesia general y extradural sobre la respuesta adrenocortical a la operación de cesarea de tipo electivo o de emergencia. Las concentraciones de cortisol en el plasma materno se midieron antes de la operación, durante ésta y a los 30 y 60 min de efectuar la incisión en la piel. También se determinaron durante el parto las concentraciones de cortisol en el plasma de la vena y de la arteria umbilical. Las concentraciones de cortisol en el plasma materno, para aquellas pacientes que recibieron anestesia extradural no cambiaron de forma significativa con relación al grupo de control en ninguno de los intervalos de tiempo. En el grupo de anestesia general, y para las operaciones de cesaria electiva, tuvo lugar un incremento significativo de las concentraciones a los 30 y a los 60 min despues de la incisión, y a los 60 min de efectuada la incisión para las operaciones de emergencia. No hubo diferencia significativa entre las concentraciones medias de cortisol en el plasma de la vena y arteria umbilical, en comparación con, ni entre los grupos de anestesia general y extradural. La anestesia extradural, en contraposición a la anestesia general, disminuye la respuesta adrenocortical a las operaciones de Cesarea mediante el bloqueo de las rutas neurogénicas aferentes que parten del emplazamiento quirúrgico. El método utilizado para anestesia no influye la respuesta de cortisol del feto.

Br. J. Anaesth. (1980), 52, 1033

EFFECTS OF CONCENTRATION OF LOCAL ANAESTHETIC DRUGS IN EXTRADURAL BLOCK

D. B. SCOTT, J. H. MCCLURE, R. M. GIASI, J. SEO AND B. G. COVINO

SUMMARY

An increase in the concentration of bupivacaine from 0.5% to 0.75% and etidocaine from 1.0% to 1.5% for extradural block resulted in a more rapid onset of sensory analgesia and motor blockade, a greater frequency of adequate analgesia, a greater depth of motor block and a longer duration of sensory analgesia and motor blockade. An increase in the concentration of prilocaine from 2% to 3% failed to reveal any significant advantage. The use of the more concentrated solutions of bupivacaine and etidocaine would appear to afford significant clinical advantages in extradural anaesthesia for surgery.

On account of the thickness of the spinal nerves, and their connective tissue covering in the extradural space, high concentrations of local anaesthetic drugs are required frequently if sensory and motor blockade are to be complete following extradural administration (Galindo et al., 1975). An increase in the concentration of a local anaesthetic drug will, in general, cause a more profound block, with a more rapid onset and increased duration of anaesthesia (Littlewood et al., 1977). However, two factors limit the maximum concentration which can be used in clinical practice. First, a plateau will be reached in effectiveness related to concentration such that further increases in the strength of the solution produce little or no further increase in the degree of conduction blockade (Covino and Vassallo, 1976). Second, increasing the concentration and the dosage will lead ultimately to systemic toxicity and, perhaps, to localized neural damage.

When surgical procedures are to be performed on conscious patients, the degree of nerve blockade should be complete. In the United States, where local anaesthesia tends to be more popular than in Europe, local anaesthetic drugs are used frequently in greater concentrations than are available elsewhere. However, there are few controlled studies to assess the clinical advantages of these more concentrated solutions (Bridenbaugh et al., 1976). In the present study, three local anaesthetic agents for extradural block were compared in a double-blind study: bupivacaine 0.5% and 0.75%, etidocaine 1% and 1.5%, and prilocaine 2% and 3%. Adrenaline 1 : 200 000 was used with etidocaine, as plain solutions of the 1.5% solution are not available commercially.

PATIENTS AND METHODS

The 60 patients studied were divided into three groups of 20, each group being allocated one of the three test drugs, bupivacaine, etidocaine or prilocaine. Within each group 10 patients received the more concentrated solution and 10 the less concentrated solution. The order of administration of the drugs was randomized and the investigators carrying out the assessment of nerve blockade were unaware of the concentration given.

The 40 patients in the bupivacaine and etidocaine studies were anaesthetized at the University of Massachusetts Medical Center and the 20 receiving prilocaine were anaesthetized at the Royal Infirmary, Edinburgh. Because of minor differences in routine there were small differences between the experimental programme in the two hospitals. In the American series the patients were premedicated with either pethidine 50–75 mg or morphine 5–10 mg and hydroxyzine 50 mg. For the extradural block a volume of solution between 15 and 20 ml was used, the exact amount being that which was thought appropriate by the anaesthetist with regard to the patient's age and condition. The patients were male or female (table I). In the

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0007–0912/80/101033–05 $01.00

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TABLE I *Patient characteristics (mean and SEM)*

Drug	Age (yr)	Sex	Wt (kg)	Ht (cm)	Volume (ml)	Dose (mg)
Bupivacaine 0.5%	37.5±6 8	7M 3F	71±35	173±0.25	16.7±0.65	83.5
Bupivacaine 0.75%	47.1±6.8	7M 3F	73±6.8	173±0.25	16.8±0.9	126
Etidocaine 1.0%	33.7±6.8	5M 5F	69±5.1	168±0.25	17.4±0.75	174
Etidocaine 1.5%	38.4±5.7	7M 3F	71±7.1	170±0.25	15.5±0.8	232.5
Prilocaine 2%	46.2±3.2	10F	58±2.0	159±1.8	20	400
Prilocaine 3%	51 9±4.4	10F	67±4.0	161±1.5	20	600

Scottish series premedication comprised diamorphine 5 mg plus atropine 0.6 mg. A fixed dose of 20 ml was used for the extradural block and all these patients were female (table I).

An extradural catheter was inserted between the third and fourth lumbar vertebrae and advanced 2–3 cm into the extradural space, with the patient conscious, 1 h after premedication. After turning the patient supine and horizontal a test dose of 2% lignocaine 4 ml with adrenaline 1 : 200 000 was injected in the Massachusetts patients followed in 5 min by the main dose of the test drug. In the Edinburgh group no test dose was used.

Every 2 min the patient was assessed with regard to the spread and degree of nerve block. Analgesia was tested by pin-prick and the upper dermatomal limit noted. Motor block was assessed on a 0–3 scale where 0 = no motor block, 1 = inability to raise lower limb off the trolley, 2 = inability to flex the knee, 3 = total paralysis. Arterial pressure and heart rate were noted at each assessment. After 30 min the nerve block was assumed to be at or near its maximum and surgery was permitted.

After operation the patient was examined every 15 min to assess the regression of the block to the T12 level. The onset of analgesia was determined as the time to achieve spread to the dermatomes of T12, T10 and T6. The onset of motor block was the time to achieve a score of 1 or 2 in the degree of block as defined above, remembering that in not all patients was a score of 2 achieved.

The adequacy of analgesia was assessed by the need to provide additional analgesia or sedation during surgery. Duration of analgesia was taken as the time from injection to regression to T12—the time at which the patient undergoing abdominal surgery would require analgesia. Duration of motor block was taken as the time for the motor score to regress to 1 unit. This was not assessed in the case of prilocaine.

The results from the four groups of patients receiving either bupivacaine or etidocaine and the two groups receiving prilocaine were subjected to statistical analysis using either Student's *t* test or χ^2 test as appropriate. No comparison between prilocaine and the other two drugs was performed as different observers had been used and the experimental programmes varied slightly.

RESULTS

Sensory analgesia

The onset of analgesia is shown in table II. The onset to T12 and T10 was decreased by approximately 50% when the concentration of bupivacaine was increased from 0.5% to 0.75% ($P < 0.01$). Etidocaine 1.5% was not significantly more rapid than etidocaine 1.0%, but both solutions showed a more rapid onset than bupivacaine 0.5 and 0.75% ($P < 0.05$). There were no significant differences in the onset of analgesia between prilocaine 2% and 3%, both of which had onset times very similar to bupivacaine 0.5%.

The level of the highest dermatomes reached with the extradural blocks did not differ significantly between any of the drugs used. The spread in all the patients was adequate for the performance of lower abdominal surgery. There were no missed segments, but with bupivacaine the first sacral nerve required an average of 16–22 min for complete analgesia compared with 6–10 min with etidocaine.

TABLE II. *Onset, spread, adequacy and duration of sensory analgesia (mean and SEM).*
*Significant differences: *bupivacaine 0·5%* v. *other solutions; †bupivacaine 0·75%* v. *etidocaine 1%; ‡bupivacaine 0.75%* v *etidocaine 1.5%; §etidocaine 1.0%* v. *etidocaine 1.5%*

Drugs	Onset (min) to T12	Onset (min) to T10	Onset (min) to T6	Total spread (No. of dermatomes)	Adequacy of analgesia	Regression to T12 (min)
Bupivacaine 0.5%	8.2±1.0	14.7±1.4	17.0±1.6	15.6±0.5	60%	189.4±17.7
Bupivacaine 0.75%	4.4±0.5*	7.7±1.3*	14.2±3.0	18.0±0.7	90%	294.0±19.9*†
Etidocaine 1.0%	2.5±0.45*†	5.8±1.1*	11.7±2.4*	17.0±0.8	60%	198.5±17.2
Etidocaine 1.5%	2.5±0.2*‡	4.5±0.4*‡	9.3±1.3*‡	17.4±0.4	90%	279.0±17,9*§
Prilocaine 2%	9.5±0.9	12.5±1.1	17.0±3.4	16.8±0.85	90%	163.9±10.0
Prilocaine 3%	9.0±1.0	14.0±1.5	16.7±2.1	17.4±0.95	100%	179.6±8.6

Bupivacaine 0.5% and etidocaine 1.0% achieved analgesia requiring no additional medication in only six of the 10 patients in each group, while the more concentrated solutions achieved similar analgesia in nine of the 10 patients. In the prilocaine series the 2% solution achieved adequate analgesia in nine of the 10 patients, while analgesia was adequate in all cases in the 3% group.

Both bupivacaine 0.75% and etidocaine 1.5% produced a significantly longer duration of sensory analgesia than the less concentrated solutions ($P<0.01$). There were no significant differences between the two drugs when either the two less concentrated or the two more concentrated solutions were compared. The duration of analgesia with prilocaine was shorter than that with bupivacaine or etidocaine. The 3% solution produced analgesia with an average duration of 180 min compared with 165 min for prilocaine 2%. This difference was not statistically significant.

Motor blockade (table III)

The onset times for motor block with bupivacaine 0.75% was more rapid than with the 0.5% solution ($P<0.01$). The onset of motor block with bupivacaine 0.5% required 17.7± SEM 2.5 min and showed the greatest disparity between onset of sensory and motor blockade. All 20 patients receiving bupivacaine achieved at least a 1+ degree of motor block. However, three of the patients receiving bupivacaine 0.5% developed a 2+ degree of motor block compared with eight of the group receiving bupivacaine 0.75%. None of the bupivacaine-treated patients achieved a 3+ degree of motor blockade.

Etidocaine caused a more profound motor block than either prilocaine or bupivacaine. Nine of the 20 patients receiving either etidocaine 1% or 1.5% developed complete paralysis of the legs, and only one patient did not achieve a 2+ degree of motor block. Etidocaine 1.5% was faster in producing a 2+ degree of motor block than the 1% concentration ($P<0.01$).

Prilocaine 3% did not produce a more rapid onset of motor block than the 2% solution. The 3% concentration caused more motor block than the 2% prilocaine, but this difference was not statistically significant. Seventeen of the 20 patients in the prilocaine group had a 2+ degree of motor block.

TABLE III. *Onset, duration and degree of motor blockade (mean and SEM).*
*Significant differences. *bupivacaine 0.5%* v. *other solutions, †bupivacaine 0.75%* v. *etidocaine 1.0%; ‡bupivacaine 0.75%* v *etidocaine 1.5%; §etidocaine 1.0%* v. *etidocaine 1.5%*

	Onset (min) to 1+	Onset (min) to 2+	Regression (min)	Degree of motor block 1+	Degree of motor block 2+	Degree of motor block 3+
Bupivacaine 0.5%	17.7±2.5	17.3±2.7	149.4±16.1	10/10 100%	3/10 30%	0/10 0%
Bupivacaine 0.75%	6.5±2.0*	18.3±2.5	246±16.6*†	10/10 100%	8/10 80%	0/10 0%
Etidocaine 1.0%	7.3±1.6*	14.7±1.5	151±14.2	10/10 100%	9/10 90%*	4/10 40%
Etidocaine 1.5%	5.2±1.0*	9.0±1.0*‡	239±19.6*§	10/10 100%	10/10 100%*	5/10 50%
Prilocaine 2%	9.0±1.0	14.3±1.3	—	10/10 100%	7/10 70%	1/10 10%
Prilocaine 3%	11.0±1.25	19.0±1.45	—	10/10 100%	10/10 100%	2/10 20%

The duration of motor blockade was significantly prolonged when the more concentrated solutions of bupivacaine and etidocaine were used ($P < 0.01$). The duration of motor block increased from 149 ± 16 min for bupivacaine 0.5% to 246 ± 16 min for the 0.75% solution. Etidocaine 1% produced a motor block for 151 ± 14 min compared with 239 ± 19 min for the 1.5% concentration. In no patient did motor block outlast sensory block.

DISCUSSION

The more concentrated solutions of bupivacaine (0.75%) and etidocaine (1.5%) produced a more rapid onset of sensory analgesia and motor blockade, a greater frequency of adequate analgesia and profound motor block, and a longer duration of sensory and motor block than the more dilute solutions. An increase in the concentration of prilocaine from 2% to 3% did not appear to be associated with a significant improvement in the effectiveness of the local anaesthetic agent.

In the United Kingdom, none of the concentrated solutions is available commercially. There are clearly considerable advantages to the use of the stronger solutions of bupivacaine and etidocaine in performing surgical procedures as opposed to their use for producing analgesia, for example in labour when motor block would be undesirable.

Although all solutions produced sufficient nerve blockade to allow the performance of the planned operations, additional sedation was required in 40% of patients receiving the weaker solutions of bupivacaine and etidocaine.

No side-effects were observed with any of the anaesthetic solutions. Blood concentrations of prilocaine, bupivacaine and etidocaine were not determined in this study. Previous investigations have shown an increase in the peak venous plasma concentration of all three agents as the concentration and total dosage administered to the extradural space was increased (Covino and Vassallo, 1976). However, the plasma concentrations following extradural administration of 0.75% bupivacaine 20 ml, 1.5% etidocaine 20 ml and 3% prilocaine 20 ml appear to be well below the concentration required for c.n.s. toxicity (Scott, Jebson and Boyes, 1973; Arthur et al., 1979). The only theoretical disadvantage of the more concentrated solutions is the greater risk of toxicity if the more concentrated solution was inadvertently injected to a vein or to the subarachnoid space. The added clinical benefits which were obtained from the use of the more concentrated solutions of bupivacaine and etidocaine justify the risk against the benefit. Such is not the case with prilocaine 3%.

The increase in the strength of the solution of prilocaine does not yield the advantages seen with the other two drugs. Prilocaine 2% produces a satisfactory degree of sensory and motor block in most patients and it is the least toxic of all amide local anaesthetic drugs (Eriksson, 1966). Little additional value is obtained by using the 3% solution for extradural block. The smaller total dosage achieved with prilocaine 2% will reduce the frequency of its most irritating side-effect, methaemoglobinaemia, the severity of which has been shown to be dose-related (Lund and Cwik, 1965).

Since the 40 patients receiving either etidocaine or bupivacaine were randomized with regard to both concentration of solution and drug used, it was possible to compare the two drugs directly. Etidocaine was shown to produce a more rapid onset and a more profound degree of motor blockade. Several studies have indicated a longer duration after bupivacaine compared with etidocaine, but this was not seen in the present investigation. The addition of adrenaline to the etidocaine solutions may have been responsible for this lack of difference. No direct comparison between prilocaine and the other two drugs is strictly valid, but the similarity in duration of block of prilocaine 2% and 3% compared with bupivacaine 0.5% and etidocaine 1% is noteworthy. Since prilocaine is the least toxic of the amide-type local anaesthetic drugs while possessing highly satisfactory anaesthetic qualities, its extradural use, particularly in poor-risk patients, should be of value.

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EINIGE ASPEKTE DER ANWENDUNG GRÖSSERER KONZENTRATIONEN VON LOKALNARKOSEMITTELN BEI EXTRADURALER BLOCKIERUNG

ZUSAMMENFASSUNG

Eine Erhöhung der Konzentration von Bupivacaine von 0,5% auf 0,75%, und bei Etidocaine von 1,0% auf 1,5% bei extraduraler Blockierung führte zu einem schnelleren Einsatz sensorieller Analgesie und motorischer Blockade, einer grösseren Frequenz ausreichender Analgesie, einer grösseren Tiefe der motorischen Blockierung und einer längeren Dauer der sensoriellen Analgesie und motorischen Blockade. Eine Erhöhung der Konzentration von Prilocaine von 2% auf 3% brachte keine zusätzliche Vorteile mit sich. Die Verwendung der stärkeren Konzentrationen von Bupivacaine und Etidocaine bringt anscheinend bedeutende klinische Vorteile bei der extraduralen Narkose bei chirurgischen Eingriffen mit sich.

EFFETS DE LA CONCENTRATION DES AGENTS ANESTHESIQUES LOCAUX UTILISES POUR LE BLOCAGE EXTRADURAL

RESUME

Lorsqu'on a augmenté la concentration de bupivacaïne de 0,5% à 0,75% et celle d'étidocaïne de 1% à 1,5% pour le blocage extradural, on a obtenu un début plus rapide de l'analgésie sensorielle et du blocage moteur, une plus grande fréquence d'analgésie adéquate, une plus grande profondeur du blocage moteur de même qu'une plus longue durée de l'analgésie sensorielle et du blocage moteur. L'augmentation de la concentration de prilocaïne de 2% à 3% n'a révélé aucun avantage significatif. L'usage de solutions de bupivacaïne et d'étidocaïne plus concentrées semble devoir présenter des avantages cliniques d'une certaine importance pour le blocage extradural avant une intervention chirurgicale.

EFECTOS DE LA CONCENTRACION DE ANESTESIA LOCAL EN EL BLOQUEO EXTRADURAL

SUMARIO

Un incremento desde 0,5% a 0,75% y del 1,0% a 1,5% en la concentración de bupivacaína y de etidocaína, respectivamente, para el bloqueo extradural, tuvo como resultado un inicio más rápido de la analgesia sensorial y del bloqueo motriz, una mayor frecuencia de analgesia adecuada, una mayor profundidad del bloqueo motriz y una mayor duración de la analgesia sensorial y del bloqueo motriz. Un incremento en la concentración de prilocaína desde el 2% al 3% no reveló ninguna ventaja significativa. El uso de las soluciones de bupivacaína y de etidocaína más concentradas parece que presentan ventajas clínicas significativas en la anestesia extradural encaminada a la actividad quirúrgica.

Br. J. Anaesth. (1980), 52, 1039

COMPARATIVE EFFECTS OF INDUCED HYPOTENSION AND NORMOVOLAEMIC HAEMODILUTION ON BLOOD LOSS IN TOTAL HIP ARTHROPLASTY

G. BARBIER-BÖHM, J. M. DESMONTS, E. COUDERC, D. MOULIN, P. PROKOCIMER AND H. OLIVIER

SUMMARY

The effects of deliberate hypotension and normovolaemic haemodilution on operative blood loss were studied in patients undergoing hip arthroplasty. Thirty patients were anaesthetized with halothane–nitrous oxide, and assigned to one of three groups. In group I, mean arterial pressure was decreased to 55 mm Hg by sodium nitroprusside. In group II, 23 ± 2 ml/kg of blood was withdrawn just before the surgical procedure and replaced by twice the volume with 4% albumin and Ringer lactate solution. The shed blood was reinfused at the end of the surgical procedure. In group III, the blood replacement was equal to blood loss and this group served as control. Intraoperative blood losses were 1050 ± 185 ml and 900 ± 130 ml in the autotransfused and control groups, respectively, and 320 ± 35 ml in the hypotensive group. However, the total red cell loss was significantly less in the hypotensive and autotransfused groups than in the control group. No complications occurred in any of the three groups. Deliberate hypotension was the most effective means of reducing intraoperative bleeding and the time for this procedure was shorter than for normovolaemic haemodilution combined with autotransfusion.

Total hip replacement is associated with substantial blood loss. Techniques used to reduce intraoperative bleeding include hypotensive anaesthesia, deliberate hypotension and preoperative normovolaemic haemodilution combined with several variations of autologous blood transfusion. The advantages of decreased blood loss include better surgical conditions, improved attachment of methyl methacrylate cement to bone, and the need for less transfusion of bank blood. A recent review of the published reports on average blood loss for total hip arthroplasty (Thompson et al., 1978) showed that good results were obtained with extradural or spinal anaesthesia and deliberate hypotension. No data on the effects of haemodilution were reported in this review. However, Rosberg and others (1977) did not observe any difference in total blood loss between a haemodilution group and a control group undergoing hip surgery. We have evaluated two techniques for reducing blood loss: controlled hypotension, and normovolaemic haemodilution followed by postoperative transfusion of the shed blood. The results were compared with those observed in patients undergoing the same surgical procedure with normotensive anaesthesia.

METHODS

Thirty patients undergoing total hip arthroplasty gave informed consent for the study. None had previously undergone any surgical procedure on the hip. Patients with cardiovascular, pulmonary or renal disease were excluded. The patients were assigned to one of three groups: (1) *Hypotension with sodium nitroprusside* (group I; $n = 11$); mean arterial pressure was maintained at 55 mm Hg. The nitroprusside infusion was started before the incision and stopped before wound closure. Transfusion was started when intraoperative blood loss exceeded 300 ml. (2) *Haemodilution* (group II; $n = 9$) in which 23 ± 2 ml/kg body weight of blood was withdrawn after induction of anaesthesia but before the start of the surgical procedure. Simultaneously, the volume of shed blood was replaced with an equal volume of 4% albumin in saline, and a similar volume of lactated Ringer's solution. Intraoperative blood loss was replaced with the same mixture. At the end of the surgical procedure, the shed blood was reinfused over approximately 2 h. Additional donor blood was transfused when necessary. (3) *Control group* (group III; $n = 10$) in which operative blood loss was replaced with the same amount of homologous

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0007-0912/80/101039-04 $01.00

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blood. In all cases, the volume of blood lost was estimated during operation by weighing sponges and by measuring suction drainage, and after operation by measuring blood collected from the wound drainage. The red cell volume lost was estimated from the haematocrit.

Mean ages were 54±5, 51±3 and 55±3 yr in groups I, II and III respectively. All patients received diazepam 10 mg and atropine 0.5 mg i.m. 1 h before induction. Anaesthesia was induced and maintained with nitrous oxide 60% in oxygen, supplemented by halothane 0.5% and small doses of phenoperidine. All operations were performed by one surgeon, with the patient in the lateral position. A Wagner double-cup prosthesis was used in all cases. The attachment of the double-cup was with methacrylate cement. This procedure differs from the Charnley-type total hip arthroplasty, in that resection of the femoral head is not necessary and blood loss is reduced.

Haemoglobin concentration was measured before operation and immediately and 1, 4 and 10 days after operation. The means and standard errors were calculated for group data and comparison between groups was performed with Student's t test for unpaired data. $P<0.05$ was regarded as statistically significant.

RESULTS

The results obtained with the different methods are in table I. The smallest intraoperative blood loss occurred with controlled hypotension: 320±35 ml *v.* 1050±180 ml and 900±130 ml in the autotransfused and control groups respectively. Blood loss after operation was similar in the three groups. However, total red cell loss including losses during and after operation was not different in the hypotensive and autotransfused groups, because the intraoperative haematocrit in the latter group (23%) was less than in the hypotensive group (36%). Red cell loss in both of these groups was significantly less than in the control group (table II). However, total measured blood loss was significantly less in the hypotensive patients compared with the other groups. The criteria for blood transfusions were different in

TABLE I. *Operative blood losses (mean± SEM)* †$P<0.05$ *group I* v. *group II and* v. *group III*

	Volume of loss (ml)		
	Group I	Group II	Group III
During operation	320±35†	1050±180	900±130
After operation	460±75	400±50	530±100
Total	780±80†	1450±220	1430±150

TABLE II. *Red cell volume loss (mean*± SEM). †$P<0.01$ *group I* v. *group II;* ‡$P<0.05$ *group II* v. *group III;* §$P<0.05$ *group III* v. *groups I and II*

	Red cell volume (ml)		
	Group I	Group II	Group III
During operation	130±20†	240±40‡	350±60
After operation	150±20	110±23	180±40
Total	280±30	350±50	530±60§

TABLE III. *Blood loss and replacement in the three groups*

	Total measured blood loss (ml)	Transfused blood (ml)	Patients transfused
Hypotensive group	780±80	500±170	8/11
Auto-transfused group	1450±220	135±100	2/9
Control group	1430±150	1485±190	10/10

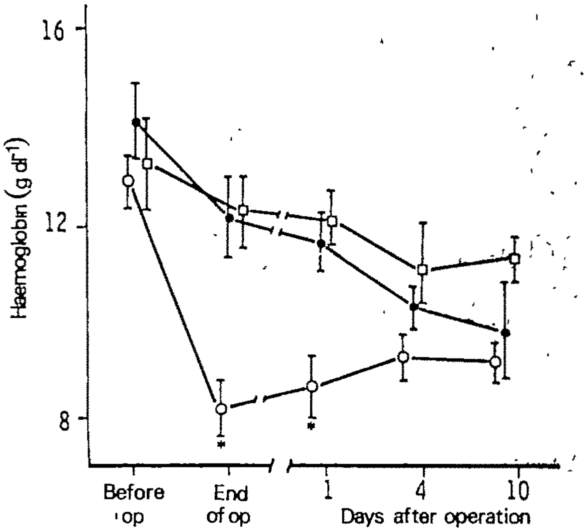

FIG. 1. Changes in haemoglobin concentration after surgery: ●—● group I induced hypotension; ○—○ group II haemodilution and autotransfusion; □—□ group III control; vertical bar = SEM. *$P<0.02$ group II *v.* group I and *v.* group III.

each group, so that comparison of the amount of transfused blood is only of incidental interest. Excessive bleeding after operation in two of the autotransfused patients necessitated banked blood transfusion (table III). Comparison of haemoglobin concentrations in the three groups revealed significantly smaller values in the autotransfused group early after operation (fig. 1). However, by the 4th day, no difference was observed in the three groups. Moderate anaemia was present in all patients on the 10th day after operation.

DISCUSSION

Our study demonstrates that deliberate hypotension to a mean arterial pressure of 55 mm Hg during hip arthroplasty was the most effective means of reducing bleeding during surgery. Similar results have been reported with nitroprusside (Lawson et al., 1976) or with deliberate hypotension induced by halothane (Thompson et al., 1978) despite the fact that different mechanisms are involved in the hypotension. Halothane produces hypotension by myocardial depression (Prys-Roberts et al., 1974) and nitroprusside by arteriolar vasodilatation (Adams et al., 1974). Comparison with other studies is difficult because of differences in the management of deliberate hypotension. Amanarath and others (1975) reported blood loss of 800 ml during surgery with nitroprusside and trimetaphan, but the intraoperative arterial pressure was reduced by only 20–30% from the value before operation. Furthermore, in this study, a correlation between blood loss and arterial pressure during operation was noted. Controversy regarding the use of deliberate hypotension stems from the possible increased risk of tissue damage from hypotension-induced hypoperfusion. In evaluating previous reports dealing with the complications of induced hypotension, it is important to consider the recent improvement in management of these patients. Hypotensive anaesthesia has been made safer and more reliable by the use of modern monitoring techniques. Thompson and others (1978) have shown that the use of deliberate hypotension for hip surgery did not affect the results of tests of cerebral, hepatic or renal function and myocardial status after operation.

Regional anaesthetic techniques also decrease blood loss during operation (Stanton-Hicks, 1971; Davis, Jennings and Harris, 1974; Sculco and Ranawat, 1975), but in a previous study from this hospital, we did not observe any difference attributable to general *v.* extradural anaesthesia (Guyochin et al., 1973).

In the present study, there was no difference between the haemodilution and control groups with respect to the total blood loss. Thus the need for homologous blood was reduced in the haemodilution group compared with the control group, because the red cell volume was significantly reduced. Patients subjected to normovolaemic haemodilution tolerated the procedure well, but Laks and others (1974) have shown that acute haemodilution resulted in a marked increase in cardiac output and in a parallel decrease in blood viscosity and total peripheral resistance. Guyton and Richardson (1961) demonstrated that the decrease in peripheral resistance resulted in increased venous return and thus increased cardiac output. This adaptation is dependent on cardiac function, which is sometimes altered in elderly patients undergoing total hip replacement. Rao, El-Etr and Montoya (1979) have shown that haemodilution-induced anaemia is not well tolerated in patients with severe coronary artery disease.

In conclusion, the best surgical conditions were achieved with deliberate hypotension, which was the most effective means of reducing intraoperative bleeding. The need for donor blood transfusion was reduced in patients undergoing haemodilution and retransfusion of fresh autologous blood. However, withdrawal of blood before operation considerably lengthened the time leading to operation and the operative field was not as dry as with deliberate hypotension. The combination of moderate intraoperative haemodilution and hypotensive anaesthesia could be suggested as the best technique for patients undergoing hip surgery.

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EFFETS COMPARATIFS DE L'HYPOTENSION PROVOQUEE ET DE L'HEMODILUTION NORMOVOLEMIQUE SUR LA PERTE DE SANG SUBIE AU COURS D'UNE ARTHROPLASTIE COMPLETE DE LA HANCHE

RESUME

Les effets d'une hypotension délibérée et d'une hémodilution normovolémique sur les pertes de sang opératoires ont été étudiés sur des patients subissant une arthroplastie de la hanche. Trente patients ont été anesthésiés à l'aide d'halothane–protoxyde d'azote et inscrits dans l'un des trois groupes suivants. Dans le Groupe I, la pression artérielle moyenne a été abaissée à 55 mm Hg à l'aide de nitroprussiate de soude. Dans le Groupe II, on a retiré 23+2 ml/kg de sang, juste avant l'intervention chirurgicale et on l'a remplacé par deux fois ce volume d'une solution lactate de Ringer contenant 4% d'albumine. Le sang prélevé a été réintroduit par perfusion à la fin de l'intervention chirurgicale. Dans le Groupe III, le remplacement de sang a été égal au sang perdu et ce groupe a servi de groupe témoin. Les pertes de sang résultant de l'opération ont été respectivement de 1050±185 ml et de 900±130 ml dans le groupe à "autotransfusion" et le groupe "témoin" et de 320±35 ml dans le groupe "hypotendus". Cependant, la perte totale de globules rouges a été nettement moindre dans les Groupes "hypotendus" et à "autotrans fusion" que dans le groupe témoin. Il ne s'est produit de complication dans aucun des trois groupes. L'hypotension délibérée a été le moyen le plus efficace de réduire les saignements se produisant au cours des opérations et le temps nécessaire à ce procédé a été plus court que celui qu'il a fallu pour l'hémodilution normovolémique combinée avec une autotransfusion.

VERGLEICHENDE WIRKUNGEN VON INDUZIERTEN BLUTDRUCKERNIEDRIGUNG UND VERDÜNNUNG MIT BLUTPLASMA-ERSATZSTOFFEN AUF DEN BLUTVERLUST BEI TOTALER HÜFTGELENKPLASTIK

ZUSAMMENFASSUNG

Es wurden Untersuchungen über die Auswirkungen von absichtlich induzierter Blutdruckerniedrigung und Verdünnung mit Blutplasma-Ersatzstoffen auf den operationsbedingten Blutverlust bei Hüftgelenkplastik angestellt. Dreissig Patienten wurden mit Halothan–Stickstoffoxydul anästhetisiert und in drei Gruppen unterteilt. Bei Patienten der Gruppe I wurde der durchschnittliche Arterienblutdruck mittels Nitroprussidnatrium auf 55 mm Hg reduziert. Bei Patienten der Gruppe II wurden 23±2 ml/kg Blut kurz vor dem chirurgischen Eingriff entzogen und durch das doppelte Volumen mit 4% Albumin und Ringer-Laktatlösung ersetzt. Das verlorene Blut wurde am Ende der Operation wieder eingeflösst. Bei Patienten der Gruppe III entsprach der Blutersatz genau dem Blutverlust und diese Gruppe diente als Kontrollgruppe. Bei den Eigenblut-infusions- und Kontrollgruppen ergaben sich intraoperative Blutverluste von 1050±185 ml bzw. 900±130 ml, und bei der Druckerniedrigungsgruppe 320±35 ml. Der Gesamtverlust an roten Blutkörperchen war jedoch bei den Druckerniedrigungs- und Eigenblutinfusions gruppen bedeutend weniger als bei der Kontrollgruppe. Bei keiner von den drei Gruppen entstanden Komplikationen. Die absichtlich induzierte Blutdruckerniedrigung erwies sich somit als die wirksamste Methode, den intraoperativen Blutverlust zu verringern und das Verfahren dauerte auch nicht so lang wie die Blutverdünnung mit Blutplasma-Ersatzstoffen und anschliessender Eigenblutinfusion.

EFECTOS COMPARATIVOS DE LA HIPOTENSION INDUCIDA Y DE LA HEMODILUCION NORMOVOLEMICA EN RELACION A LA PERDIDA SANGUINEA EN LA ARTROPLASTIA TOTAL DE LA CADERA

SUMARIO

Se estudiaron los efectos de la hipotensión deliberada y de la hemodilución normovolémica relativas a la pérdida sanguinea, en pacientes sometidos a artroplastia de la cadera. Se anestesiaron 30 pacientes con óxido nitroso–halotano y se les asignó a uno de los tres grupo. En el grupo I, la presión arterial media se disminuyó hasta un valor de 55 mm Hg por medio de nitrato prúsico de sódio. En el grupo II, se extrajeron 23±2 ml/kg de sangre justo antes de llevar a cabo la operación quirúrjica y se sustituyeron mediante el doble del volumen extraido con un 4% de albúmina y una solución 'Ringer' de lactato. La sangre extraida se reintegró al término del proceso quirúrjico. En el grupo III, la sangre sustituida igualó a la

pérdida, y este grupo sirvió como control. Las pérdidas intraoperativas de sangre fueron de 1050 ± 185 ml y de 900 ± 130 ml en los grupos de control y de autotransfusión, respectivamente, y de 320 ± 35 ml en el grupo de hipotensión. No obstante, la pérdida total de glóbulos rojos fue significativamente inferior en los grupos de hipotensión y de autotransfusión que en el grupo de control. No tuvo lugar complicación alguna en ninguno de los tres grupos. La hipotensión provocada fue el medio más efectivo de reducir el derrame de sangre intraoperativo y el tiempo de duración de este proceso fue más corto que para la hemodilución normovolémica combinada con autotransfusión.

Br. J. Anaesth. (1980), 52, 1045

SODIUM NITROPRUSSIDE-INDUCED HYPOTENSION IN RADICAL THORACO–ABDOMINAL DISSECTION OF RETROPERITONEAL LYMPH NODES

J. A. STIRT, E. L. KORN AND R. C. REYNOLDS

SUMMARY

Blood loss and replacement in 57 consecutive otherwise healthy young patients undergoing radical thoraco–abdominal dissection of retroperitoneal lymph nodes is reviewed. Twenty-five patients received nitroprusside (hypotensive group); 32 patients (normotensive group) did not. Blood loss varied significantly between the hypotensive and normotensive groups: the mean loss (±SEM) was 920±72 ml for the hypotensive group compared with 1341±98 ml for the normotensive group ($P<0.001$). The total blood requirement for the normotensive patients was three times that of the hypotensive group. The difference between the two groups was more apparent in patients with advanced disease.

Although deliberate hypotension is utilized occasionally as an adjunct to anaesthesia, there are few objective assessments of its benefits. Several studies of nitroprusside-induced hypotension have appeared recently, reporting experience in total hip arthroplasty (Amaranath et al., 1975; Lawson et al., 1976; Thompson et al., 1978), spinal fusion (Anderson, 1978; Khambatta et al., 1978), and oral–facial corrective surgery (Schaberg et al., 1976). We record here our experience with sodium nitroprusside-induced hypotension in a retrospective evaluation of radical thoraco-abdominal dissection of retroperitoneal lymph nodes, the first report of the effects of nitroprusside hypotension on blood loss and replacement in non-peripheral surgery.

METHODS

Hospital records of all patients undergoing radical thoraco–abdominal dissection of retroperitoneal lymph nodes, performed by the same surgeon with the same group of anaesthetists from 1973 to 1978, were examined and only the 57 patients whose operations were confined strictly to dissection of lymph nodes were included. Twenty-five patients received sodium nitroprusside (hypotensive group), and 32 patients did not (normotensive group). The decision to use hypotension was made by the individual anaesthetist at the time of operation.

Patients were men in ASA physical status I or II with diagnoses of testicular carcinoma in stages A, B or C. Patients were anaesthetized with halothane, enflurane, or narcotics with nitrous oxide and oxygen and the lungs were ventilated mechanically. Fluid management during operation consisted of maintenance fluids (Ringer's lactate or physiological saline, or both) 125–250 ml h^{-1}, and replacement of losses (less than 10% blood volume loss replaced with crystalloid (Ringer's lactate or physiological saline, or both), 10–20% loss replaced with crystalloid and colloid (5% albumin or purified plasma protein fraction, or both), and greater than 20% loss replaced with blood).

All patients were placed in the same modified flank–10° Trendelenberg position during surgery. Arterial pressures were recorded from the radial artery in the dependent arm in all hypotensive patients and in 50% of the normotensive patients; the others were monitored using an arterial pressure cuff on the dependent arm. Blood loss was recorded on the anaesthetic record by the anaesthetist every 30 min during the surgical procedures, and consisted of contents of suction bottle less irrigation fluid, plus visual estimation of blood in sponges, tapes and drapes, with an allowance made for irrigation fluid.

Means were compared using two-tailed t tests; proportions were compared using Yate's corrected Chi-square statistics (Snedecor and Cochran, 1967).

RESULTS

Mean ages, weights, ASA status, stage of disease, and preoperative mean arterial pressures and

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0007–0912/80/101045–04 $01.00

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haematocrits were not significantly different in the two groups (table I). All patients in the hypotensive group had either halothane or enflurane anaesthesia. In 66% of those in the normotensive group anaesthesia was maintained with one of these two agents, and the remaining 34% received narcotics. In the normotensive group there were no significant differences in the indices noted between patients anaesthetized with different techniques (table II).

TABLE I. *Values before operation (mean ± SEM). *The hypotensive and normotensive groups were not significantly different at $P<0.05$ level for any value. †Stage A: confined to the testicle; stage B. retroperitoneal lymph node metastasis; stage C: metastasis above the diaphragm or to solid viscera, brain or bone*

	Hypotensive*	Normotensive*
Number of patients	25	32
Age (yr)	26.5 ± 1.1	29.9 ± 1.6
Weight (kg)	73.8 ± 1.8	77.7 ± 2.0
Disease stage A†	13	20
Disease stage B	11	11
Disease stage C	1	1
Mean arterial pressure before operation (mm Hg)	106.9 ± 2.0	106.2 ± 1.6
Haematocrit before operation (%)	44.8 ± 0.4	45.5 ± 0.5

TABLE II. *Normotensive group: effects of anaesthetic technique (mean values ± SEM). *The enflurane/halothane and nitrous oxide/narcotic groups were not significantly different at $P<0.05$ level for any value*

	Enflurane or halothane	N_2O/narcotic*
Number of patients	21	11
Mean arterial pressure during operation (mm Hg)	97 ± 2	105 ± 4
Blood loss (ml)	1382 ± 137	1264 ± 117
Blood replacement during operation (ml)	667 ± 187	591 ± 222
Total blood replacement (ml)	714 ± 184	727 ± 227

In the hypotensive group, mean arterial pressure during hypotension was 68 mm Hg, a decrease of 33 mm Hg from the pressure during anaesthesia before the induction of hypotension (fig. 1). The duration of deliberate hypotension ranged from 45 to 215 min, with a mean of 139 min. The dose of nitroprusside ranged from 5 to 90 mg (mean 46 mg).

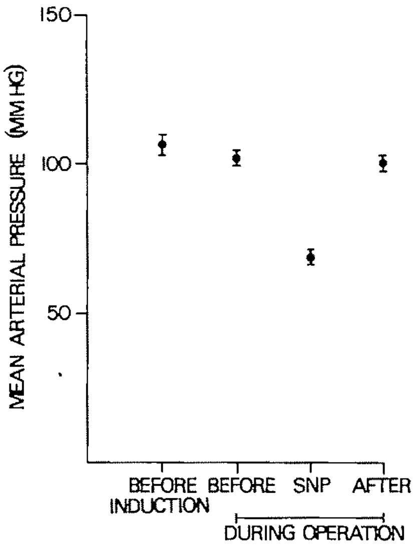

FIG. 1. Change in arterial pressure (±1 SD) during the administration of sodium nitroprusside ($P<0.01$). Pressures before SNP and after SNP were not significantly different ($P<0.1$).

Blood loss during surgery varied significantly between the hypotensive and normotensive groups: the mean loss was 920 ± 72 ml in the hypotensive group as a whole and 1341 ± 98 ml in the normotensive group. Twelve per cent of all patients in the hypotensive group received blood during operation, compared with 38% of the normotensive group. Further examination of the total perioperative (intra-operative plus postoperative) period revealed that 32% of the hypotensive group required blood transfusion compared with 50% of the normotensive group. The hypotensive group received an average of 0.48 unit (400 ml) of blood per patient, compared with 1.44 unit per patient in the normotensive group (fig. 2).

The duration of surgery and change in haematocrit (from value before operation to the smallest value after operation) did not differ significantly in the two groups (table III). Blood loss and replacement were analysed by stage of disease, and the differences between the two groups were found to increase with severity of disease (table IV, fig. 3).

DISCUSSION

A commonly-used criterion for transfusion in otherwise healthy patients is to replace any blood loss exceeding 20% of estimated blood volume.

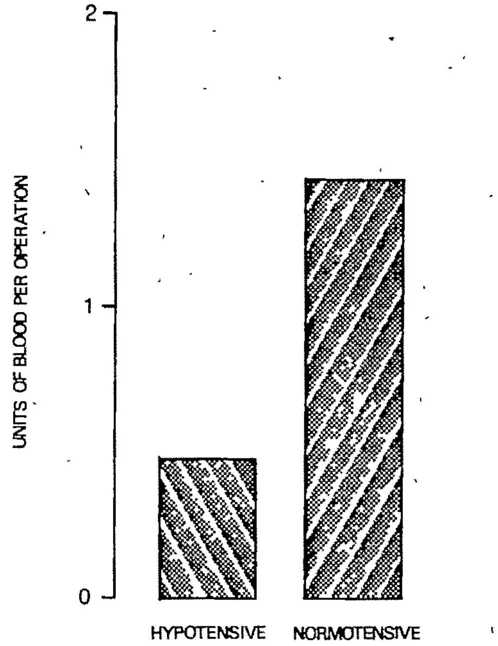

FIG. 2. Blood transfusion: units per operation in all patients. The 25 patients receiving nitroprusside (hypotensive group) received 0.48 unit per operation, and the 32 patients in the normotensive group received 1.44 unit per operation.

TABLE III. *Duration of surgery and change in haematocrit (mean values ± SEM). *The hypotensive and normotensive groups were not significantly different at* P < *0.05 level*

	Hypotensive	Normotensive
Duration of surgery (min)*	247 ± 7	250 ± 7
Change in haematocrit (%)*	−13.6 ± 1	−14.3 ± 9

TABLE IV. *Blood loss and replacement: by disease stage (mean values ± SEM). *Hypotensive and normotensive groups differed significantly* (P < *0.01*)

	Hypotensive	Normotensive
Blood loss stage A* (ml)	788 ± 87	1082 ± 97
Blood loss stage B* (ml)	1034 ± 111	1756 ± 145

Assuming an estimated blood volume of approximately 5 litre (75 kg average weight × 70 ml blood volume kg^{-1}), the average patient would begin receiving blood when blood loss approached or exceeded 1000 ml.

The average blood loss in patients receiving nitroprusside was 920 ml; normotensive patients had an average loss of 1341 ml. Many patients in the hypotensive group had a blood loss of 10–20% of total blood volume, and some had less than a 10% blood loss. In these patients, transfusions and their associated risks could be avoided safely, and blood volume maintained with crystalloid and colloid solutions. Thus, the significant decrease in blood loss in the hypotensive group resulted in a lesser requirement for blood replacement (fig. 2).

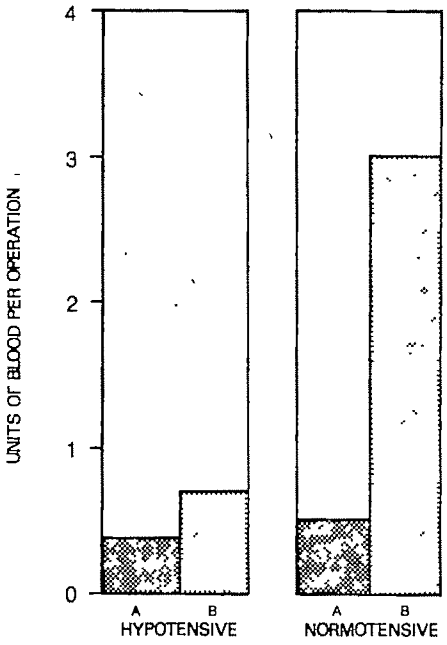

FIG. 3. Blood transfusion: unit per operation in different disease stages. Patients with limited (stage A) disease received 0.38 unit per operation when hypotension was used, compared with 0.50 unit per operation without hypotension. Patients with metastatic disease (stage B) received 0.64 unit per operation with hypotension, compared with 3.00 unit per operation without hypotension.

There was no significant difference between the hypotensive and normotensive groups in the decrease in haematocrit after operation, from preoperative values. This suggests that both groups were transfused using the same criteria, since need for blood replacement after operation was determined by the surgical staff in all cases. The duration of surgery did not vary significantly when hypotension was used.

Each unit of blood carries a risk of complications. Therefore, blood transfusion was evaluated in terms of the number of units used per patient, in addition to the number of patients transfused. The average exposure rate per patient to a unit of transfused blood was three times greater in the patients in the normotensive group than for patients in the hypotensive group. The difference was largely a result of the markedly greater need for transfusion in patients with metastasis (fig. 3).

ACKNOWLEDGEMENTS

The authors thank Dr Donald G. Skinner, Associate Professor of Surgery and Urology, UCLA School of Medicine, Los Angeles, California. Without his encouragement and co-operation, this study would not have been possible.

The study was supported in part by a grant from the UCLA Department of Anesthesiology.

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HYPOTENSION PROVOQUEE PAR LE NITROPRUSSIATE DE SODIUM AU COURS D'UNE DISSECTION RADICALE THORACO-ABDOMINALE DES GANGLIONS LYMPHATIQUES RETROPERITONEAUX

RESUME

On passe en revue dans cet article les pertes de sang subies, et le remplacement de ce dernier, par 57 jeunes patients consécutifs, qui étaient à part cela en bonne santé et qui ont subi une dissection radicale thoraco-abdominale des ganglions lymphatiques rétropérinéaux. Vingt-cinq d'entre eux ont reçu du nitroprussiate de sodium (groupe hypotendu); alors que les trente deux autres n'en ont pas reçu (groupe normotendu). Les pertes de sang ont varié d'une manière significative entre le groupe hypotendu et le groupe normotendu: la perte moyenne (± écart type des moyennes) a été de 920 ± 72 ml pour le groupe hypotendu, alors que pour le groupe normotendu celle-ci a été de 1341 ± 98 ml ($P < 0{,}001$). Les besoins totaux en sang pour les patients du groupe normotendu ont été trois fois plus grands que ceux du groupe hypotendu. La différence entre les deux groupes a été plus apparente chez les patients ayant une maladie à un stade avancé.

NATRIUMNITROPRUSSID-BEWIRKTE HYPOTENSION BEI RADIKALER BRUST-UNTERLEIBS SEKTION DER RETROPERITONEALEN LYMPHKNOTEN

ZUSAMMENFASSUNG

Untersucht wird Blutverlust und Ersatz bei 57 sonst gesunden jungen Patienten bei radikaler Brust-Unterleibs Entfernung der retroperitonealen Lymphknoten. Funfundzwanzig Patienten erhielten Nitroprussid (hypotensive Gruppe); 32 Patienten (normotensive Gruppe) nicht. Der Blutverlust variierte wesentlich bei beiden Gruppen: der mittlere Blutverlust (±SEM) betrug bei der hypotensiven Gruppe 920 ± 72 ml, verglichen mit 1341 ± 98 ml bei der normotensiven Gruppe ($P < 0{,}001$). Der gesamte Blutbedarf für die normotensiven Patienten war dreimal so hoch wie für die andere Gruppe. Bei Patienten mit fortgeschrittener Krankheit waren die Unterschiede zwischen beiden Gruppen ausgeprägter.

HIPOTENSION INDUCIDA MEDIANTE NITROPRUSIATO DE SODIO, EN DISECCION TORACICO-ABDOMINAL RADICAL DE LOS NUDOS LINFATICOS RETROPERITONEALES

SUMARIO

Se analiza la pérdida de sangre y la restitución de ésta en 57 pacientes consecutivos, sanos en demás aspectos, sometidos a disección torácico-abdominal radical de los nudos linfáticos retroperitoneales. Veinticinco de los pacientes recibieron nitroprusiato de sodio (grupo con hipotensión); 32 de los pacientes (grupo de presión normal) no lo recibieron. La pérdida de sangre varió de forma significativa entre ambos grupos: la pérdida media (± desviación típica) fue de 920 ± 72 ml para el grupo con hipotensión en comparación con 1341 ± 98 ml para el grupo de tensión normal ($P < 0{,}001$). La necesidad total de sangre para el grupo de tensión normal fue tres veces superior a la del grupo con hipotensión. La diferencia entre los dos grupos fue más evidente en los pacientes con enfermedad avanzada.

Br. J. Anaesth. (1980), 52, 1049

ON BEING AWARE BY REQUEST

A Mother's unplanned request during the course of a Caesarean section under general anaesthesia

M. E. TUNSTALL

SUMMARY

A patient became wakeful during a general anaesthetic for Caesarean section. The isolated forearm technique for assessing wakefulness was in use: In response to questioning, the patient indicated by hand signals her wish to remain awake. She felt no pain. After the operation she was able to remember the experience, being told about the delivery, and hearing her baby cry. The words from a tape-recording of the anaesthetist's postoperative visit on the next day are presented.

Awareness is an accepted term in anaesthesia which signifies that a patient has remembered being awake during an operation under a general anaesthetic (Parkhouse, 1960). When awake, the patient, immobilized by a neuromuscular blocking drug, is usually unable to indicate her plight. If, on the other hand, the neuromuscular blocking drug is prevented from reaching one forearm by a pneumatic tourniquet on the upper arm, she can make signals with her hand. This is called the isolated forearm technique (IFT) for assessing wakefulness (Tunstall, 1979). A patient who is wakeful during an operation but has no recall after the operation is said not to have suffered awareness; she has experienced amnesic wakefulness.

A recent editorial in the *British Journal of Anaesthesia* (1979) gave an account of a mother who suffered greatly from her experience of awareness. This could have been prevented if the anaesthetist routinely used IFT for Caesarean sections under general anaesthesia.

This case report is presented as a reminder that wakefulness is not necessarily associated with suffering (Artusio, 1955). However, the events in this report were entirely unplanned and had never been entertained previously. Deliberate attempts to recreate the same conditions during another section could go seriously wrong and are not recommended.

CASE REPORT

The patient was 40 years old and nulliparous, with increased arterial pressure who, becoming wakeful during the course of a general anaesthetic for Caesarean section, signalled her wish to remain awake.

At the preoperative visit the patient said she would prefer a general anaesthetic to either the subarachnoid or extradural block which was offered. IFT was discussed, but she already knew of its routine use in the hospital; her husband was a member of the medical staff. The anaesthetic induction sequence was: hydrallazine 20 mg i.v., 3 min inhalation of 99.5% oxygen and 0.5% halothane, IFT, thiopentone 300 mg and suxamethonium 100 mg, cricoid pressure, and endotracheal intubation. Maintenance anaesthesia was provided with a mixture of halothane 0.4%, nitrous oxide 33% in oxygen (12 litre min^{-1} non-rebreathing) and suxamethonium 400 mg h^{-1}i.v. In the 2–4 min from the commencement of the thiopentone injection the nitrous oxide was increased to 66% as she was wakeful at 2 min and 3 min (moving IFT hand on instruction).

The abdominal incision was made at 8 min and she became wakeful again at 10 min. She denied feeling any discomfort. As her hand signals were so calm and her response to questioning so prompt and consistent, she was asked if she wanted to be more deeply anaesthetized. The answer was no. Asked if she wished to remain awake as she was, she replied yes. Questions were repeated several times and the signalling codes reversed several

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0007-0912/80/101049-03 $01.00

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times so that the anaesthetist was certain of her wishes. She was given a running commentary shortly before delivery. She heard the baby cry at delivery and was told its sex.

The clarity of the patient's level of wakefulness, and its relatively prolonged duration, raised the suspicion that postoperative recall of these events was a distinct possibility.

The postoperative interview the next day was recorded on tape. Extracts are reported:

Anaesthetist (*A*). Do you remember breathing the oxygen before going to sleep?

Patient (*M*). Yes, I do, and you said it would take about three minutes.

A. And did you feel at all drowsy while you were breathing the oxygen?

M. I felt pleasantly relaxed.

A. And the actual moment of going to sleep, what was that like?

M. Just a fading out.

A. And what was the next thing you remember after that?

M. As far as I can remember—if you hear me, squeeze my fingers. I am not absolutely certain about this, whether it was once for yes and twice for no or the other way round.

A. Yes, Well, I can assure you your instructions were very clear and accurate. And did you feel any discomfort at all?

M. None whatsoever.

A. None. Do you remember me asking you about that?

M. Yes.

A. Yes. You said last night you were concerned that I should know you were all right.

M. That's right. Yes. Yes, that was very strong.

A. You had a very strong desire to let me know that everything was all right?

M. Yes.

A. Because I asked you several times if you wanted to be made more sleepy, more anaesthetized, or made unconscious.

M. I can quite distinctly remember saying "No, I'm fine, no, I'm fine".

A. Well, I felt a little bit of anxiety about the situation because normally when somebody indicates that they are wakeful I deepen the anaesthetic. I then asked you again—Are you quite happy, and you said Yes, so I didn't change the nitrous oxide, and then I asked whether you wished to stay as you were and you indicated very clearly that you did. So I took courage in both hands and didn't deepen the anaesthetic.

M. Oh! Super!

A. ... Because I thought, well, if the patient wishes to stay as she is I'll let her remain as she is. Though it did cause me some anxiety; but your hand was calm in between the times I was holding it. It wasn't waving about saying "help". Your husband was in the gallery watching your hand, which increased my anxiety just a little bit more (laughter), and then I kept in contact with you every minute or so. I told you the baby was coming quite soon, and then just before the baby was born I let the cuff down so that I could just concentrate on the various bits and pieces that had to be done. But I did speak to you about the baby. You then couldn't signal with your hand, but I indicated that everything was all right. And then after the baby was born I said "Now, I am going to put you right off".

M. I can remember you saying that, and then it was just nothing.

A. Are you glad that you heard the baby cry?

M. Yes, absolutely.

A. That's all right. Because basically I was doing what you asked me to do.

M. That's right. Yes, and this is what is so extraordinary. I can remember wanting to get this message across very, very strongly.

A. Well, I still feel apprehensive about it, but I am just delighted it went that way.

DISCUSSION

A disadvantage of a standard obstetric anaesthetic technique is that it does not cater for biological variation. At one end of the scale the mother receives more anaesthetic than she needs. At the other the mother suffers awareness. IFT is so simple and practical that it can be used for most emergency, and elective, operative deliveries under general anaesthesia. In patients with pre-eclampsia and under sedation, for example, the anaesthetist can often afford to cut-back on the gaseous and volatile anaesthetic agents during Caesarean section if he can determine whether the mother is wakeful or not.

The case reported is quite exceptional and was entirely unplanned. This patient who was relatively resistant to anaesthetics, under different environmental circumstances, could have suffered extreme mental distress. Whenever light anaesthesia is being used with neuromuscular blocking drugs conversation in the operating theatre should always be considerate. In patients on the verge of wakefulness inappropriate remarks could trigger off nightmares. Nightmares can be worse than frank awareness as they can recur, and the victim has to live through them repeatedly.

The deliberate promotion of awareness when myoneural blockers are being used cannot be justified, except in highly specialized circumstances, such as scoliosis surgery (Abott and Bentley, 1980). The mother who wishes to be awake during a Caesarean section should be offered either a subarachnoid or extradural block, or in rare instances local infiltration analgesia.

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LE FAIT DE RESTER CONSCIENT SUR SA PROPRE DEMANDE

Demande non prévue d'une mère au cours d'une opération césarienne effectuée sous anesthésie générale

RESUME

Une patiente s'est éveillée dans le courant d'une opération césarienne effectuée sous anesthésie générale. On utilisait à ce moment là la technique de l'avant-bras isolé pour déterminer le degré de reprise de conscience. En réponse aux questions qui lui ont été posées, la patiente a indiqué, par des signes faits avec les mains, qu'elle souhaitait rester consciente. Elle ne ressentait aucune douleur. Après l'opération, elle a été à même de se souvenir de cette expérience, à savoir d'être tenue informée de la délivrance et d'avoir entendu son bébé crier. On présente dans ce document les paroles de l'anesthésiste qui avaient été enregistrées sur bande le lendemain, lors de sa visite post-opératoire.

ÜBER DIE BEWUSSTHEIT AUF WUNSCH. DER UNGEPLANTE WUNSCH EINER MUTTER WÄHREND EINES KAISERSCHNITTS BEI ALLGEMEINNARKOSE

ZUSAMMENFASSUNG

Bei einer Schnittentbindung wurde die Patientin trotz Allgemeinnarkose wieder wach. Zur Bestimmung des Bewusstseinsgrades wurde die Technik des isolierten Unterarms verwendet. Auf Anfrage hin machte die Patientin durch Handzeichen klar, dass sie wach bleiben wollte. Sie empfand keine Schmerzen. Nach Abschluss der Operation konnte sie sich noch an den Ablauf der Operation erinnern, wie sie uber die Entbindung unterrichtet wurde und wie das Kind geweint hat. Der Wortlaut einer Bandaufnahme, die bei dem postoperativen Besuch des Anasthetisten am folgenden Tage gemacht wurde, wird beigefugt.

SOBRE EL PERMANECER CONSCIENTE BAJO SOLICITUD

Solicitud no planeada por parte de una madre durante el transcurso de una sección de cesárea, bajo anestesia general

SUMARIO

Una paciente se despertó durante el proceso de anestesia general encaminado a efectuar una sección de cesárea. Se usó la técnica de antebrazo aislado para evaluar el grado de consciencia. En respuesta a las preguntas efectuadas la paciente indicó mediante señales manuales su deseo de permanecer despierta. No sintió daño alguno. Después de la operación fue capaz de recordar la experiencia, de lo que se le dijo sobre el nacimiento y de haber escuchado los llantos del bebé. Se presenta la grabación en una cinta, de la conversación de la visita postoperativa del anestesista efectuada al día siguiente.

THIRD SURGIKOS TRAVEL AWARD

The Surgikos Division of Johnson & Johnson are inviting applications for the 1980 Surgikos Travel Awards for Consultant Surgeons and Anaesthetists.

The Travel Awards, which are supported by the Association of Surgeons of Great Britain and Ireland and the Association of Anaesthetists of Great Britain and Ireland, are valued at £1200.

The Award scheme was started in 1978 to assist Consultant Surgeons and Anaesthetists to undertake research in the U.K. or abroad. Previous winners have travelled to Canada, Germany, Holland and France to prepare their research.

The subject chosen by an applicant should be concerned with an advance in surgical or anaesthetic knowledge and have some application within the National Health Service. Successful applicants will be required to submit a report in a form which would be suitable for publication.

Surgeons and Anaesthetists who wish to apply for a Surgikos Travel Award should write for an entry form to:

The 1980 Surgikos Travel Award for Consultants,
2, Seaforth Place,
Buckingham Gate,
London S.W.1.

CRITICAL CARE MEDICINE SOCIETY OF SOUTHERN AFRICA
THIRD NATIONAL CONGRESS

Johannesburg May 13–16, 1981

Topics: bioengineering; cardiac function in the critically ill; metabolism; nursing; paediatrics; respiratory function; shock; trauma.

Invited speakers: Dr Jeremy Swan (Los Angeles, U.S.A.); Dr Gillian Hansen (London, England); Dr A. B. M. Telfer (Glasgow, Scotland); Dr Robert Wright (Sydney, Australia).

Information: The Organizing Committee,
Department of Anaesthesia,
Johannesburg Hospital,
Private Bag X39,
Johannesburg 2000,
South Africa.

CANZ 1981

CONFERENCE OF ANAESTHETISTS OF NEW ZEALAND

The Scientific Meeting of the combined New Zealand Society of Anaesthetists and Faculty of Anaesthetists will be held in the Clinical School, Wellington Hospital, on May 21–24, 1981.

Further information from:
Department of Anaesthesia,
Wellington Hospital,
Private Bag,
Wellington,
New Zealand.

THIRD WORLD CONGRESS ON PAIN

(SPONSORED BY THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN)

September 4–11, 1981 Edinburgh, Scotland

Further information: Third World Congress on Pain,
University of Edinburgh,
Centre for Industrial Consultancy and Liaison,
16 George Square,
Edinburgh, EH8 9LD.

or Louisa E. Jones, B.S., Executive Secretary,
International Association for the Study of Pain,
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Br. J. Anaesth. (1980), 52, 1055

CORRESPONDENCE

MASS SPECTROMETERS IN ANAESTHESIA

Sir,—We were interested to read the article by Davis and Spence (1979). We have been using a similar technique for some time applied to a V.G. Micromass Q701B mass spectrometer, and in the light of our experience we were surprised to see an apparent overall accuracy of 1% of gas concentration reported in the article.

We performed a computer simulation in an attempt to evaluate the "worst-case" measurement errors in the system used at the University Hospital of South Manchester. This simulation was based on the observed cracking pattern of the mass spectrometer, and the mathematical attributes of the peak splitting unit, automatic sensitivity control and analog chart recorder. This type of evaluation was adopted because of the difficulty of assessing all the errors present when multifactorial mixtures are measured during respiration. The following equations relate the electronic outputs observed at the relevant mass numbers (peak heights) to the concentrations of the various gases present. These were used to establish a first approximation to the "effective" cracking pattern of our Q701B.

$$\begin{aligned}
\text{Peak } 28 &= (1.0\times[N_2])+(0.05\times[CO_2])+(0.05\times[N_2O]) \\
\text{Peak } 30 &= (1.0\times[N_2O])+(0.015\times[N_2])+0.015 \\
\text{Peak } 32 &= (1.0\times[O_2])+(0.03\times[N_2O]) \\
\text{Peak } 117 &= (1.0\times[\text{Hal}]) \\
\text{Peak } 44 &= (1.0\times[CO_2])+(0.6\times[N_2O])+(0.1\times[\text{Hal}]) \\
&\quad +(1\times0.03)+(0.0055\times\theta) \\
\text{Peak } 12 &= (1.0\times[CO_2])+(0.2\times[\text{Hal}])+(0.3\times0.03) \\
&\quad +(0.012\times\theta)
\end{aligned}$$

where

$$\theta = [O_2^{\text{old}}]+[O_2^{\text{new}}-O_2^{\text{old}}](1-e^{-t/80})$$

for a step increase in oxygen concentration from O_2^{old} to O_2^{new}.

and

$$\theta = [O_2^{\text{new}}]+[O_2^{\text{old}}-O_2^{\text{new}}]\,(e^{-t/20})$$

for a step decrease in oxygen concentration from O_2^{old} to O_2^{new}.

where Peak = the amplitude of each peak (mV), normalized to 100 mV for 100% of the gas measured on that peak; Hal = halothane and [ ] brackets = the actual concentrations (vol./vol. %) of the appropriate gas/vapour species. As can be seen, the cracking pattern is complex, several gases contributing to most peaks. Various constants appear and reflect observed offsets on the relevant channels. The variable θ is an estimate of the carbon dioxide which is apparent subsequent to halothane sampling. This spurious carbon dioxide "production" has been observed to be critically dependent on the instantaneous oxygen concentration. The approximate time constants of 20 and 80 s have been observed for both the 44 peak and 12 peak. The peak heights which were predicted using these equations, were used as inputs to a theoretical model of our Automatic Sensitivity Control and Peak Splitter (equivalent to "S.O.E." in the article).

TABLE I. *Summary of computer error analysis*

Gas	Range of investigation	Max. error (%)	Error (% f.s.d.)
Nitrogen	0–100	+1.6 −2.4	+1.6 −2.4
Nitrous oxide	0–100	+1.2 −1.7	+1.2 −1.7
Oxygen	0–100	+1.6 −3.5	+1.6 −3.5
Carbon dioxide (44 peak)	0–5	+0.8 −1.3	+16.0 −26.0
Halothane	0–2	+0.2 −0.2	+10.0 −10.0
Carbon dioxide (12 peak)	0–5	+1.4 −0.4	+28.0 −8.0

The results of this simulation are shown in table I and suggest worst-case errors of greater than 1% (absolute). However, the peak splitter used only corrects for the contribution of nitrous oxide at peak 44 and the contributions of nitrous oxide and carbon dioxide at peak 28. The correction made by Davis and Spence for the halothane contributions at the 12 peak and 44 peak is obviously an important difference. However, this would only significantly reduce the carbon dioxide errors.

Since all possible parameters affecting this accuracy are difficult to assess and may even be machine-dependent, it would be interesting to know the figures ascribed to the various contributions by other users of Mass Spectrometers. It would also be useful to see the results of applying similar simulations to the evaluation of other machines.

The authors will be happy to supply full details of the equations used in the simulation, on request.

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NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE

Sir,—I read with great interest the recent paper of Payne, Hughes and Al Azawi (1980) on neuromuscular blockade by neostigmine.

Hardegg (1952) found that small doses of prostigmine blocked cholinesterase activity, while large doses of prostigmine occupied the acetylcholine receptors directly. In this way a neuromuscular blockade may be established as described by Payne and co-workers. Gallamine possibly dislodges prostigmine in part from the receptor site and facilitates the reappearance of acetylcholine at the receptor.

E. Gebert
Bod Nevenahr-Ahrweiler,
Germany

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Payne, J. P., Hughes, R., and Al Azawi, S. (1980). Neuromuscular blockade by neostigmine in anaesthetized man. *Br. J. Anaesth.*, **52**, 69.

Sir,—Dr Gebert presents an interesting hypothesis to explain our observations, but the work to which he refers (Hardegg, 1952) is concerned primarily with *in vitro* studies of the inhibition of erythrocyte cholinesterase by neostigmine and offers no experimental evidence to support the suggestion that large doses of neostigmine occupy the cholinergic end-plate receptors directly and so cause block.

First, it must be emphasized that we did not use large doses of neostigmine in our experiments to obtain neuromuscular block; doses of the order of 30–35 μg kg^{-1} were sufficient. Second, the block obtained was antagonized by gallamine and enhanced by suxamethonium and must therefore be classified as depolarizing in nature.

The experimental evidence which has recently been reviewed in depth by Hobbiger (1976) is consistent with the view that inhibition of acetylcholinesterase by neostigmine largely accounts for the action of the drug and the simplest explanation is that neostigmine produces an acetylcholine-induced depolarization block by preventing the destruction of the transmitter at the motor end-plate. Certainly, there can be little doubt that this inhibition is responsible for both the twitch potentiation and for the tetanic fade after the administration of neostigmine demonstrated in our paper.

In the case of the single twitch response, while it is difficult to explain potentiation on the basis of receptor occupation by neostigmine, it is easily explained by the inhibition of acetylcholinesterase which allows acetylcholine access to nerve terminals from whence it triggers repetitive antidromic nerve action potentials and thus increased twitch tensions. This phenomenon, which was first demonstrated by Brown, Dale and Feldberg (1936), can be abolished by tubocurarine in doses that have no effect on normal twitch tension. The fact that, in our patients gallamine reduced the potentiated twitch response, confirms that the interaction is not specific to tubocurarine but probably can be demonstrated for all competitive blocking agents, and strengthens the argument in favour of a competitive action with acetylcholine.

Similarly, gallamine's ability to abolish tetanic face and to restore normal tetanic wave forms during neuromuscular block by neostigmine reflects the antagonism between competitive and depolarizing neuromuscular blocking agents first highlighted by Paton and Zaimis in 1952, but previously implied by the work of Briscoe (1938), who showed that neostigmine could produce block in muscles rapidly tetanized and that tubocurarine in subparalytic doses could restore normal transmission.

Thus, available evidence supports the view that neuromuscular block induced by neostigmine is a result of the inhibition of acetylcholinesterase by the drug and of the consequent accumulation of acetylcholine at the neuromuscular junction.

J. P. Payne
R. Hughes
S. Al Azawi
London

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BOOK REVIEWS

Controversy in Anaesthesia. Edited by J. E. Eckenhoff Published by W. B. Saunders, Philadelphia. Pp. 310; illustrated; indexed. Price £13.00.

"Experts" with opposing views present the pros and cons of a variety of controversial topics. Although he is now Dean of Northwestern University Medical School, Chicago, Illinois, Dr Jim Eckenhoff is an experienced clinical anaesthetist whose collaboration with the late Dr R. D. Dripps from Philadelphia is well known. Furthermore, he has spent some time at East Grinstead Hospital with Dr Hale Enderby. Some of the choices may surprise British anaesthetists. Should inhalation equipment be aseptic for each case? Arguments on both sides are inconclusive, but provide food for thought Perhaps we, in the United Kingdom, find the problem less pressing because of our widespread use of high flow non-rebreathing techniques which does not carry the risk of a low-flow closed-circuit system.

It is noted that physicians from other disciplines have not considered anaesthetic equipment to be a real source of morbidity and mortality, otherwise we would have heard about it. One recalls the complaints by physicians and surgeons about halothane, which may in part have stimulated anaesthetists to do some serious research into the dangers. A recognized expert on that topic, Dr Burnell R. Brown jr, from the University of Arizona College of Medicine, Tucson, considers that halothane hepatitis is a "reasonably well proven clinical entity", although he is aware of its rarity. He supports this with a review of recent work on reduction metabolites and on susceptible animal models. Dr David L. Bruce from the University of California, Irvine, puts up a less convincing argument that the relationship is unproved. He concludes that "if liver toxicity can follow the use of halothane, it is the result of atypical, completely unpredictable, metabolism of the drug". Recent work from the writer's department would support Brown's view; an appreciable number of patients were found to develop abnormal enzyme activity following repeat administration of halothane, while such changes were rare in a comparable series of patients anaesthetized with enflurane. Although a clear picture is beginning to emerge, we may not yet have heard the end of the halothane controversy.

It is also unlikely that this book contains the last word on the affects of inhalation agents on reproduction. Dr Ellis Cohen, from Stanford University Medical Center, argues convincingly that inhalation anaesthetics cause genetic defects, abortions and miscarriages in operating room personnel. The opposng view, that trace concentrations of anaesthetic are not proven health hazards, is presented by Dr Louis L. Ferstandig from Hylocarbon Laboratories Inc., and in the main criticizes the epidemiological studies on the basis of flaws in their design. Some British anaesthetists have not taken this hazard seriously, and while many are prepared to spend money on expensive scavenging systems, few take the alternative of closed-circuit anaesthesia.

The choice of anaesthesia for coronary bypass operations is unlikely to be considered a point of discussion in Britain. The two opposing viewpoints, that "halothane anaesthesia is preferable to morphine" and that "balanced anaesthesia using morphine, neuromuscular blockers and nitrous oxide is the technique of choice" are not as irreconcilable as they may seem, as the editor has pointed out, "when the resources and talents exist to gather the needed data, the controversy is solvable". Similarly we would not find the use of tracheal intubation in children less than 1 year of age to be a point of contention. Nor would there seem to be much disagreement as to the necessity of tracheal intubation in parturients, although one must agree with the editor that "mandatory tracheal intubation may not be in either the patient's or physician's best interest." One must not assume that the British anaesthetist's practice is less prone to controversy than that in North America. We have differing views on the role of antacids in labour and in the place of spinal techniques, and there is a great variation in the extent to which local techniques are used in different centres.

Nor is controversy limited to scientific topics. A non-convincing case is made for allowing nurse anaesthetists to perform regional blocks in the absence of an anaesthetist A physician-anaesthetist and an educational consultant from the council for accreditation of nurse anaesthetists' education programmes for schools of the American Association of Nurse Anesthetists dispute as to who should control nurse training, although both agree that there should be anaesthetist participation in nurse anaesthetist training. This dispute may, at first, seem to be an attempt by a responsible group to control their own affairs, similar to the controversy (in the U.K.) as to importance of a self-controlled independent college of Anaesthetists in contrast to a surgically dominated college By coincidence, Eckenhoff's book opens with a chapter on surgeons and the "Captain of the Ship" doctrine, which few would consider an issue of debate. It is pointed out that both work as part of a team that also encompasses the nursing services and other supporting staff. Despite controversy on some techniques, and even principles of anaesthesia, we would all applaud this view.

John W. Dundee

Lung function, Assessment and Application in Medicine, 4th edn. By J. E. Cotes. Published by Blackwell Scientific Publications. Pp. 605; illustrated, indexed. Price £26 20.

When I began my training in pulmonary physiology about 20 years ago, the specialty was the province of a few erudite fellows who made up the membership of a fairly small club. In those days the only readable book was Comroe's classic treatise and there was an obvious need for a manual for the budding clinical respiratory physiologist. The earlier editions of this book provided, for the first time, a theoretical text and a practical manual for those concerned with the assessment of lung function. This new edition is essentially a reference book containing a wealth of material on the traditional methods used to evaluate lung function. The book has been extended to include newer methods for the assessment of airway calibre and the control of ventilation. One of the best known and highly valued features of previous editions, the section on normal values (renamed reference values) has been expanded and the reference values for adult females brought up to date. It is noticeable, however, that while new developments are mentioned in the text they are given nothing like the extensively detailed description of the traditional techniques. Notable is the superficial account of the Wagner–West multiple gas V/Q distribution technique. The widely used Konno and Mead technique for measuring chest wall mechanics is not mentioned and the $P_{0.1}$ technique for measuring respiratory drive is dismissed in a few lines. Respiratory drive measured as dP/dt max is described as the maximal rate of *increase* of pressure at the start of inspiration made against a breathing valve. This should presumably be the rate of *decrease* of pressure. Factors limiting maximal rates of airflow are discussed, but relevant new studies of the role of the downstream segment and the Wave Speed Theory of flow limitation are not mentioned. The effect of large airway obstruction on the shape of the flow–volume curve is not illustrated and the basis of the "volume of iso-flow" test using air and helium is not discussed.

It is clearly very difficult to maintain the balance of the text in successive new editions when there is an increasing number of new techniques that demand inclusion. When Dr John Cotes taught me the technique of arterial puncture almost 20 years ago it was a major procedure, but nowadays this is almost a routine clinical procedure which hardly justifies the two-and-a-half pages of text devoted to the subject in this edition. In addition to a disproportion in the treatment of old and new methods, there are some problems in the organization of the material. This may not be a particularly great problem if the book is intended only as a reference work, but gives rise to difficulty if used as a primer. For example, the strategy for assessment of the response to broncho-dilators (p. 109) appears before the section on the body plethysmograph (p. 115) and well before the section on bronchomotor tone (pp. 147, 404).

This is an essential text for those setting up or running a pulmonary function laboratory and for those in search of a clear description of the classical techniques in clinical respiratory physiology. The section on lung function in disease is excellent and is of undoubted interest to physicians and anaesthetists. Despite the wealth of recent references, this book is not recommended for those who wish to find out the modern view on how the lungs function.

J. G. Jones

Respiratory Intensive Care Nursing, 2nd edn from Beth Israel Hospital, Boston. Edited by Martha L. Morrison. Published (spiral-bound paperback) by Little Brown Co., Boston. Pp. 399; illustrated; indexed. Price £7.50.

The rapid changes in intensive respiratory care over the past 5 years have necessitated the production of the 2nd edition of this book, first published in 1973.

This has proved a worthwhile exercise and has resulted in an excellent manual which fulfils the requirements of a comprehensive text suitable for qualified nurses undertaking further training in the specialty. As stated in the preface, much of the information presented is the policy, practice and experience of a Respiratory Surgical Intensive Care Unit of the Beth Israel Hospital. This is reflected in the text, much of which is the work of nurses active in the clinical field, with contributions from an anaesthetist and a surgeon. The blend of theory and practice allows the reader to assimilate the large amount of information presented without too much difficulty. The material is well researched and clearly presented and there is a useful bibliography at the end of each chapter. It might have been helpful to have additional references within the text. Theoretical information is well presented. Professor Bushnell's contributions on the anatomy and physiology of the respiratory system are excellent. His chapter on respiratory failure is brief but helpful. Respiratory failure is defined as the need for artificial ventilation—a very practical view, although it is defined in physiological terms elsewhere. The chapter on fluid, electrolytes and acid-base disturbance is excellent, but too detailed for most nurses.

The remainder of the book consists of contributions from nursing staff. We particularly liked the discussion of nursing care in respiratory failure which combined essential procedures with humanity. The need for adequate sleep was appreciated. The problems of the mechanically ventilated patient and the indications for weaning are discussed in a helpful and practical way, obviously written by nurses aware of all the implications. We would endorse their plea to distinguish between comatose and paralysed patients and that muscle relaxants should not be given without sedatives or narcotics. It is of interest to learn that barbiturate intoxication is the most common cause of coma. It is not now so in the United Kingdom, and probably reflects differences in the prescribing patterns. This is a well balanced although short chapter which stresses the value of general supportive therapy in the treatment of drug overdosage.

The problems of control of infection in an intensive care environment are clearly discussed. It is a subject of great importance which usually receives scant attention in textbooks.

This is an excellent handbook for nurses in intensive care units and is an admirable book on which to base a nurse training programme. There is the inevitable overlap as in all multiple authorships, but much of the information can bear repetition. The editor and authors are to be congratulated. It is published in paperback, spiral binding form, on good quality paper and is extremely good value at £7.50.

I. Cooper
J. G. Mone

Annual Reports in Medicinal Chemistry, Vol. 14. Edited by J.-J. Hess. Published by Academic Press Inc. (London) Ltd. Pp. 357; illustrated; indexed. Price £11.40.

This volume aims to provide brief, critical summaries of highlights of recent literature in the fields of chemistry, pharmacology, biochemistry and medicine for those interested in the discovery and development of new drugs. The contributors are mostly from the drug industry—many of them American. The content is factual, informative and well referenced with an excellent section on drugs affecting the central nervous system. Unfortunately, much of its content will be of little immediate relevance to most clinicians.

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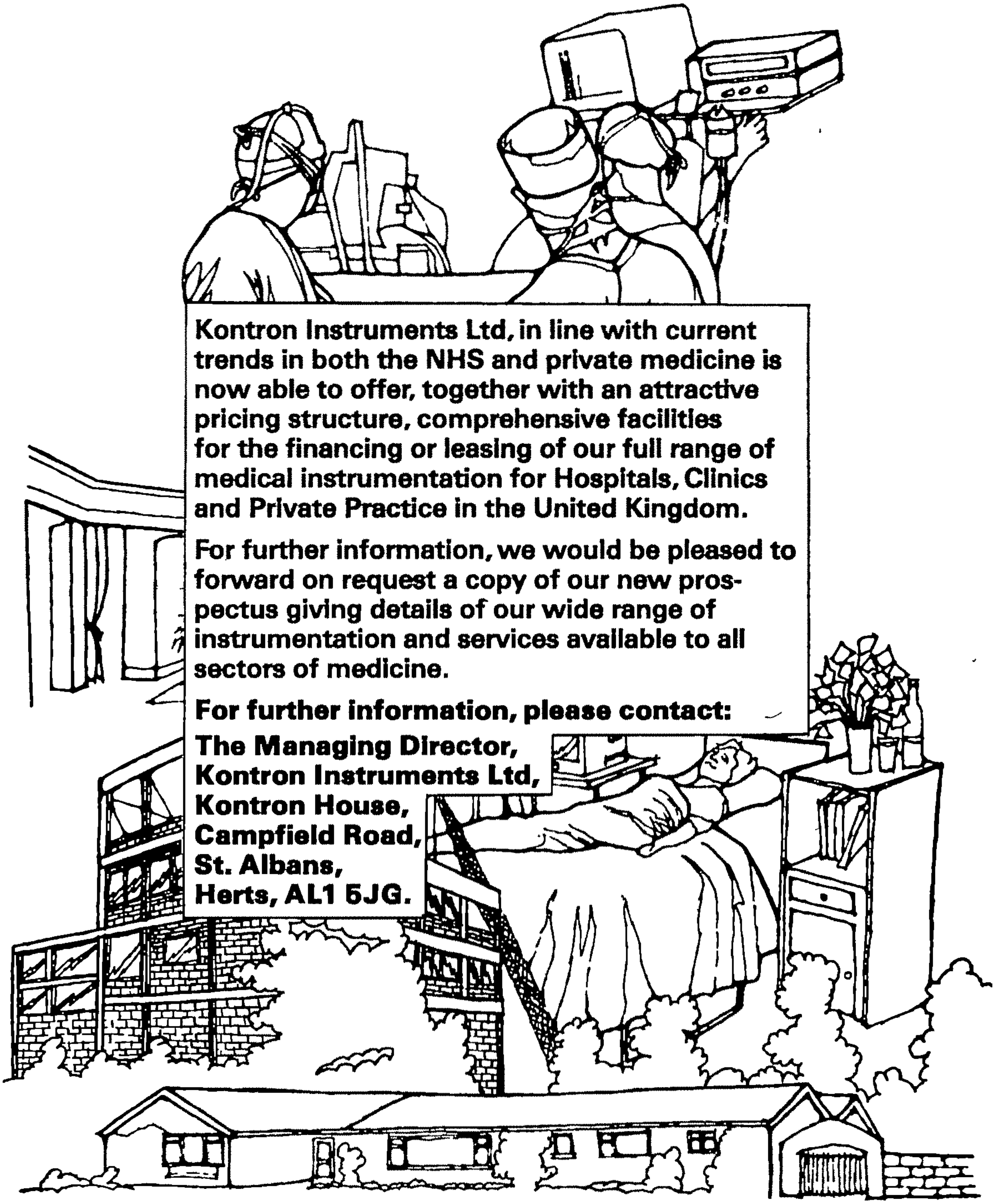

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Annual subscriptions (post free): U.K. £27.50; U.S.A. and Canada U.S.$65, Airmail U.S.$155; Rest of World £33.00, Airmail £65 ISSN 0007–0912

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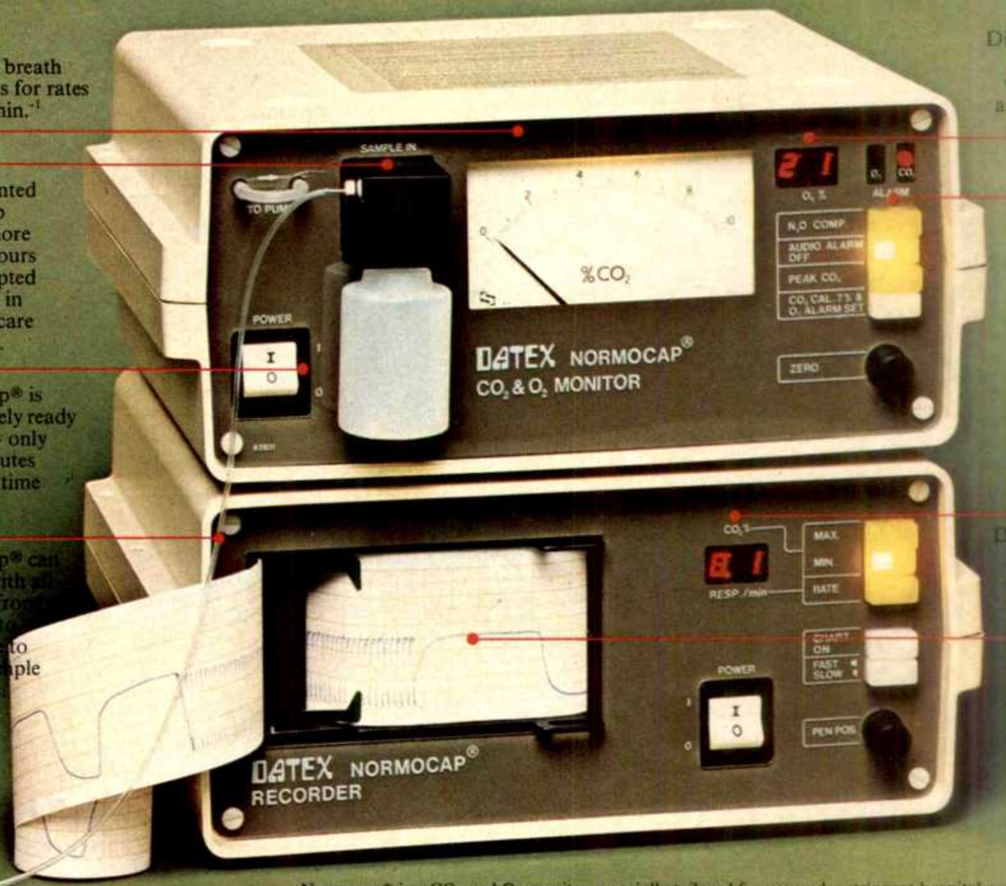

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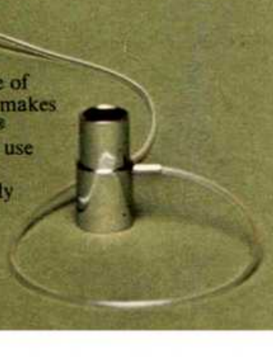

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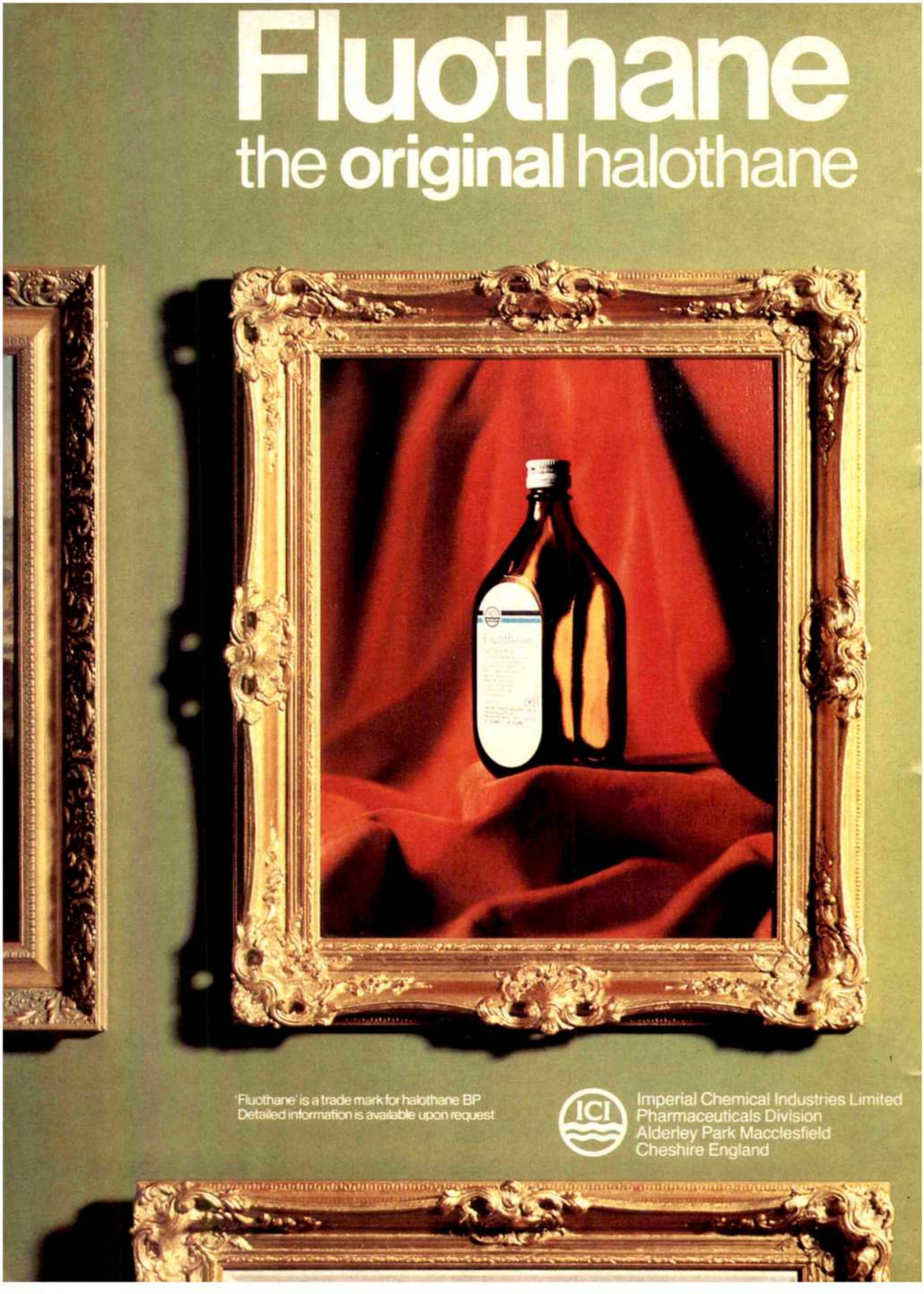

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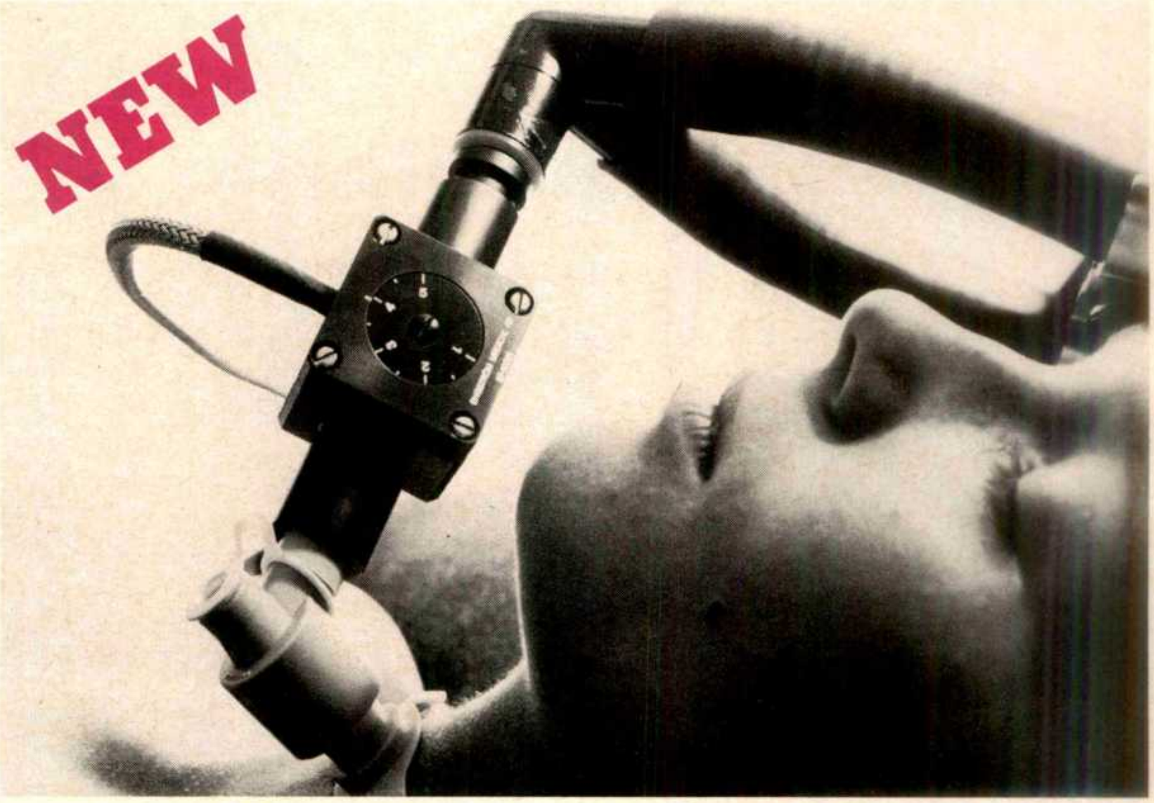

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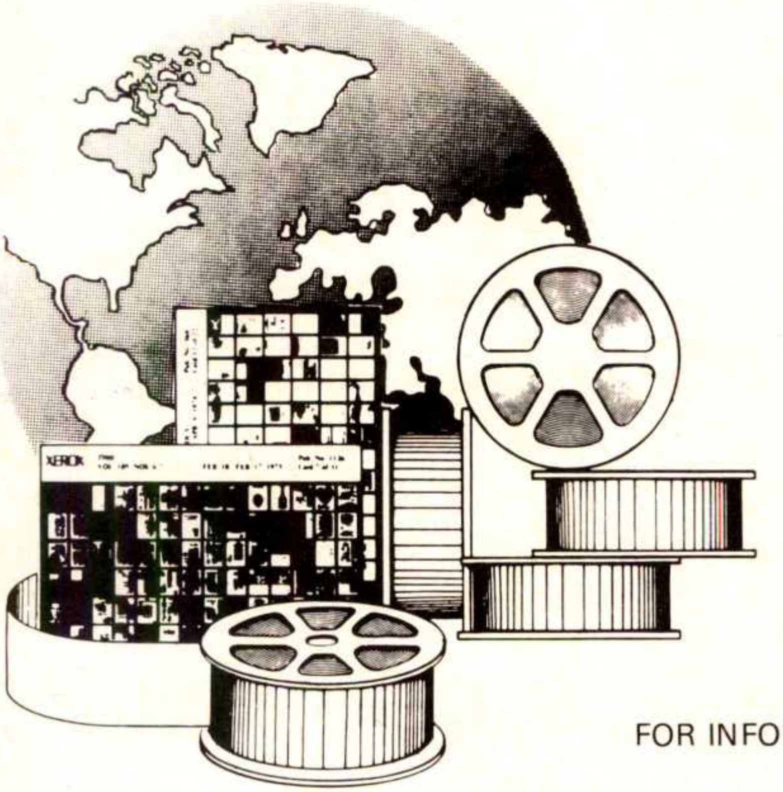

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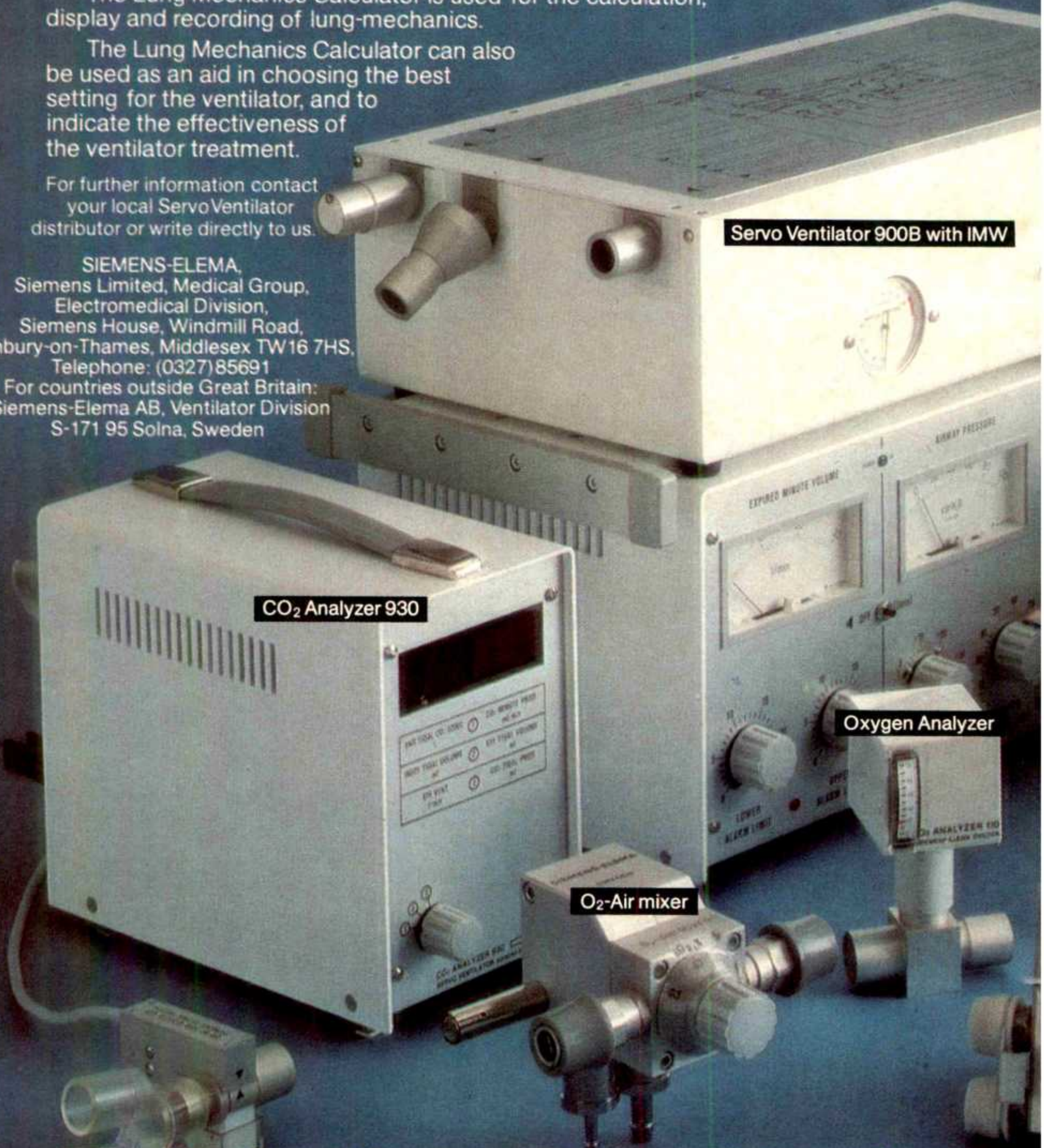

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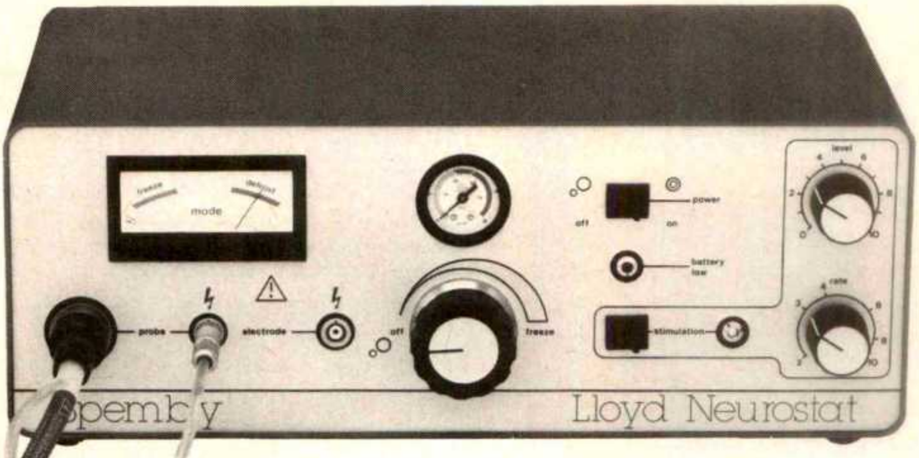

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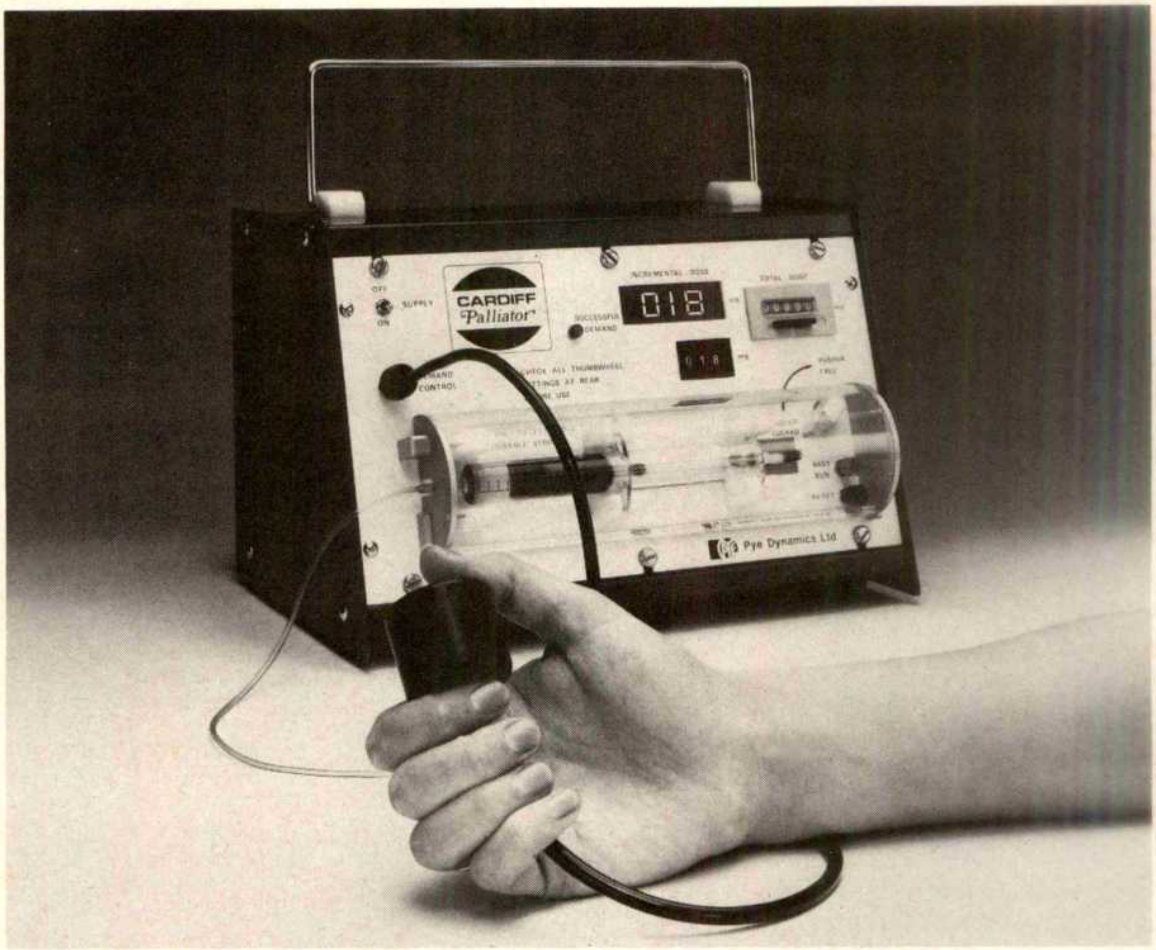

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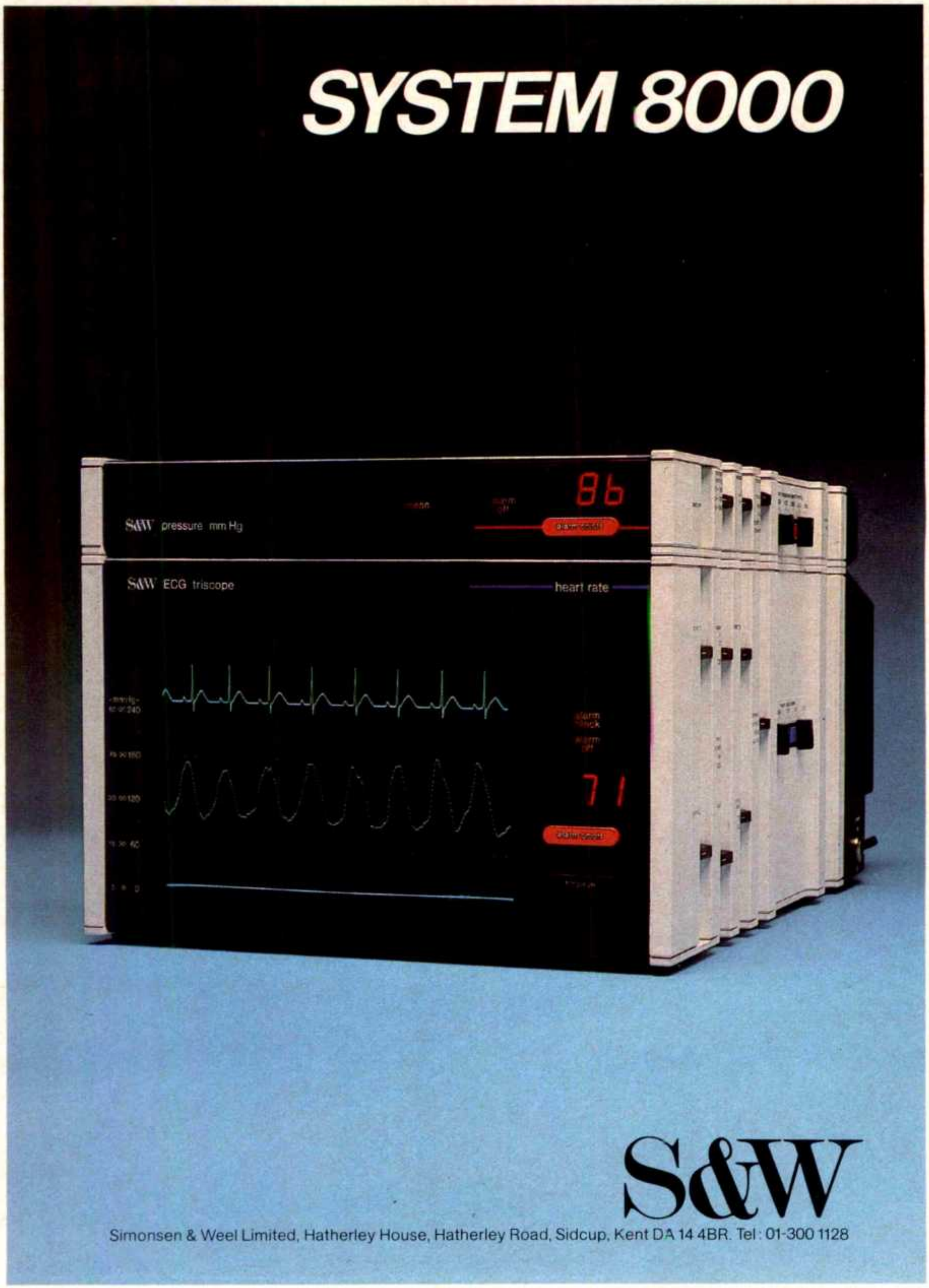

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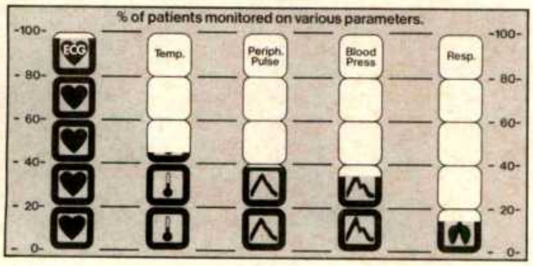

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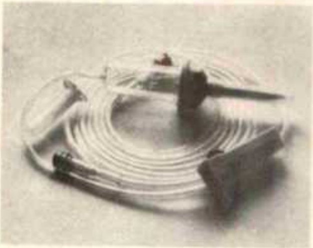

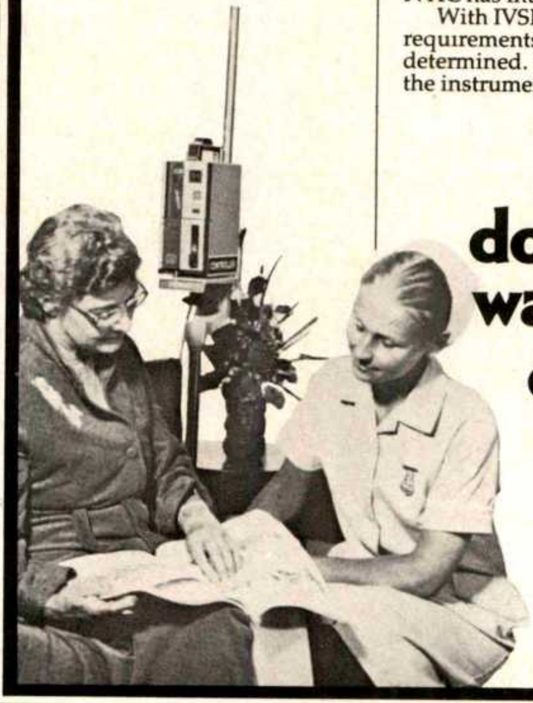

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1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
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VOLUME 52, No. 11 NOVEMBER 1980

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EDITORIAL

DRUG REACTIONS AND THE LIVER

The recent history of drug toxicity is a history of catastrophe which began with thalidomide and gained momentum with practolol. An international symposium on drug reactions and the liver was organized in July 1980 by the liver unit at King's College Hospital, London to consider hepatic drug toxicity with particular emphasis on the prediction of individuals at risk and the development of newer, safer drugs. Its aim was to co-ordinate the various approaches of clinicians, basic scientists and members of the pharmaceutical industry towards the adverse reactions of drugs to the liver.

The liver has a limited response to drug injury, but because of its central role in metabolism it is one of the principal targets for toxicity and is involved in approximately 10% of cases reported to the Committee on Safety of Medicines (Davis, 1980). Ways in which toxicity might be manifest include interference with bilirubin conjugation or excretion; cholelithiasis; dose-dependent reactions such as acute toxic hepatitis or fatty liver; dose independent (idiosyncratic) reactions such as diffuse hepatocellular damage or cholestatic hepatitis; chronic hepatitis and fibrotic lesions as well as liver tumours.

It is likely that some "idiosyncratic" reactions are predictable and that only the severity is idiosyncratic. Individual differences in metabolism via hepatotoxic derivatives may be important in this respect.

Most adverse reaction reporting results from clinical suspicion. This is very sensitive for unusual events, but has the disadvantage that the doctor must see more than one case, that false positives may result and no data on frequency are produced. Post-marketing surveillance such as that by the Committee on Safety of Medicines or the Boston Collaborative Drug Surveillance Programme does produce data on frequency and concentrates reports, but it results in under-reporting, ambiguity and may miss new types of toxicity. National mortality figures produce information from a large population and may detect rare events, but they are insensitive if the disease caused is common and they rely upon the accuracy of death certification. The problems of practolol toxicity led to registered or monitored release of new drugs. However, the best indicator of adverse reactions to drugs remains the good randomized controlled trial which provides a complete record of circumstances with valid controls and may demonstrate the increased frequency of even a common disease. The only disadvantages are the cost and the fact that large numbers may require to be studied for prolonged periods.

Attempts at randomized controlled trials of halothane have suggested an association between repeated halothane anaesthesia and increased concentrations of aminotransferases, but most of all they have demonstrated the difficulty in finding valid controls for this type of study (Wright et al., 1975). This halothane-associated hepatitis is hepatocellular with no evidence of cholestasis and may be differentiated histologically from viral hepatitis only by the presence of granulomata, eosinophils, fat and confluent necrosis. In this respect it is similar to isoniazid- and methyldopa-induced hepatitis. Nevertheless, there is a remarkable histological similarity between hepatic drug injury and primary hepatic disease. In short, halothane-associated hepatitis is well established, but the specificity is not accepted.

The ingenious animal models of halothane hepatitis (Brown and Sipes, 1977) which involve induction of the hepatic microsomal enzymes before exposure to halothane in anaesthetic concentrations in 14% oxygen may at last throw some light on the subject and allow predictions of patients at risk. Of particular interest is the fact that N-acetyl cysteine or cysteamine will protect the animals from hepatic damage if given up to 6 h after the halothane anaesthesia. These similarities to paracetamol-induced hepatic damage and its treatment are striking and should yield pointers for future research. Unfortunately the applicability of these animal models to man has not yet been established. However, it seems likely that a reduced metabolite of halothane is implicated in the aetiology of the hepatitis and that enzyme induction accounts in part for the variability in reponse of the liver to the insult. Again in animals, there is a correlation between concentrations of cytochrome p450 enzymes and liver damage and there is an increase in the concentration of urinary fluoride (an end product of the reductive pathway) when liver injury follows halothane anaesthesia.

In man there is evidence of lipid peroxidation in the liver during and for 2 h after breathing 1–1.5% halothane. This does not occur with ketamine or enflurane anaesthesia. Mild hepatic changes may occur in one in five patients after halothane and immune mechanisms are not involved. Antibodies are not detectable in patients' sera.

Severe hepatic necrosis probably has a frequency of 1 in 20 000–35 000 and is associated with antibody production and eosinophilia. It seems likely that oxidized halothane metabolites alter the antigenicity of the hepatocyte membrane, resulting in immunological attack by circulating antibodies directed towards the altered hepatocytes, and that genetic factors may influence this immunological attack. Products of the reductive pathway result in direct toxicity by covalent binding.

However, the problems of halothane-associated anaesthesia must be kept in perspective. Halothane is far down the list of causes of anaesthetic mortality and has an excellent safety record. Hypersensitivity reactions to anaesthetic drugs in general kill more patients than halothane hepatitis. Although mild reversible changes in aminotransferases following halothane are probably more common than previously suspected and may follow the first exposure to the drug, aspirin prescribed in high doses (2 g per day) for rheumatic fever, rheumatoid arthritis or systemic lupus erythematosis results in increased concentrations of aminotransferases in 48% of patients. This has resulted in much less attention from doctors.

The concept of the "silver therapeutic bullet" is long gone and has been replaced by a continuous search for the "lead lining". Anaesthetic agents are no different from other drugs in this respect.

Walter S. Nimmo

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BLOOD-GAS TENSION MEASUREMENT IN ANAESTHESIA BY BUBBLE EQUILIBRATION AND MASS SPECTROMETRY

W. W. Mapleson, B. A. Willis and B. Williams

SUMMARY

If a small bubble of gas is equilibrated with a volume of blood the partial pressures of the components of the bubble after equilibration approximate to the original tensions in the blood. A method is described in which the bubble is analysed by a respiratory mass spectrometer connected to a mini-computer The normal respiratory monitoring function of the mass spectrometer need be interrupted for only 20 s for each sample and the complete equilibration and analysis procedure takes only 3 min Theoretical studies, experimental tests and records of experimental usage show that, in a subject anaesthetized with halothane in nitrous oxide and oxygen, tensions can be measured with an overall SD of 5% for carbon dioxide and halothane and, with certain reservations, an SD of about 3% for nitrous oxide.

A multi-channel mass spectrometer can monitor simultaneously all the components of the respired gases during anaesthesia. Therefore, it is an attractive proposition to use the same instrument to make occasional measurements of all the blood-gas tensions if this can be done during brief interruptions in the respired gas measurements.

Direct measurement with an intravascular catheter (Wald et al., 1970; Lundsgaard, Groenlund and Einer-Jensen, 1978; Foëx et al., 1979) does not meet the above requirement because the mass spectrometer may take some minutes to stabilize after changing between the respiratory and blood-gas modes of operation. In addition, the response time to halothane is several minutes with existing catheters (Roberts et al., 1975; unpublished observations in this department) and, in the light of the work of Fielding and Salamonsen (1979a, b), it is difficult to foresee any improvement in response time.

An alternative is the method in which a small bubble of gas is equilibrated with a sample of blood so that the partial pressures in the bubble after equilibration approximate to the tensions in the blood before equilibration; then analysis of the gas bubble provides an estimate of the original blood-gas tensions. This method was developed by Krogh (1908) and refined by Riley and his co-workers (Riley, Proemmel and Franke, 1945; Riley, Campbell and Shepard, 1957) for the determination, by chemical analysis of the bubble, of oxygen and carbon dioxide tensions in the arterial blood of patients breathing air. It has been extended to the determination, by gas chromatographic analysis, of nitrous oxide (Bowes, 1964) and of cyclopropane and halothane (Flook, 1968). Therefore, although the method is known to be unreliable for oxygen at high values of $P\text{O}_2$, such as are often encountered during anaesthesia, it may be expected to work for the other gases present, at least the more-soluble ones. Accordingly, when a requirement arose (Mapleson et al., 1980) for the monitoring of the respired gases and the occasional determination of the tensions of halothane and carbon dioxide in the arterial blood of dogs anaesthetized with halothane and nitrous oxide in oxygen, the bubble-equilibration method was explored.

For the mass spectrometric analysis of the bubble Strang's (1961) technique was rejected because it involves switching to a special sampling mode. Instead, the bubble was analysed by injecting it into a continuous stream of "carrier" gas which was being sampled by the mass spectrometer in the ordinary "respiratory" mode. In this way the only switching was between two respiratory sampling catheters, one to sample the respired gases and one to sample the carrier gas. Thus monitoring of the respired gases was interrupted for only 20–30 s.

The technique developed for the present, specific application and the results obtained are described in detail below, with some comments on other applications and techniques.

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0007-0912/80/111061-10 $01.00

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TECHNIQUE

A 5-ml all-glass syringe with a freely-moving, flat-ended plunger was modified by distorting the bottom of its barrel to provide a conical deadspace of about 0.2 ml. A nylon three-way tap was fixed to the nozzle with epoxy resin (fig. 1A).

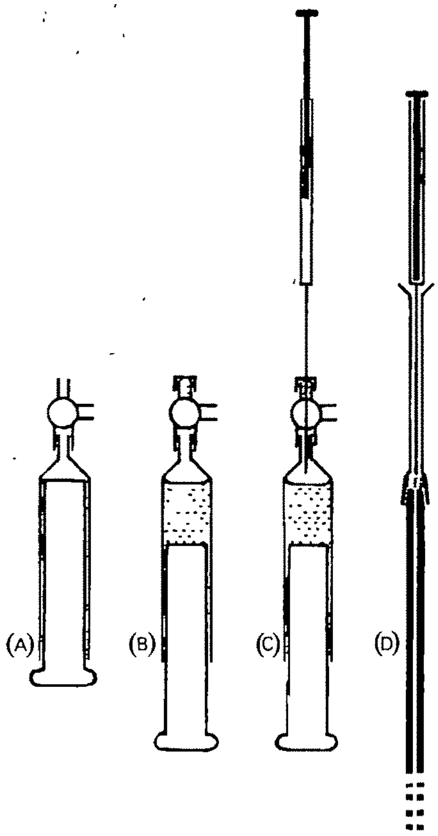

FIG 1. The bubble equilibration and analysis procedure. (A) Modified 5-ml all-glass syringe with deadspace flushed with the appropriate gas mixture. (B) Syringe with blood sample, capped ready for equilibration (C) Equilibrated gas being sampled by a 100-µlitre gas-tight syringe. (D) Gas sample injected into the bottom of a reservoir tube (actually a syringe needle) of length 110 mm, bore 1.7 mm, capacity 250 µlitre on the end of the mass-spectrometer sampling capillary. Note the two layers of filter (Millipore type HA, 0.45-µm pore size) in the hub of the wide-bore needle.

For each analysis the unlubricated syringe was flushed, first with heparinized saline containing some Matburn antifoam, then with air to expel surplus liquid, and then with the nitrous oxide–oxygen mixture which was being delivered to a halothane vaporizer, and thence to the animal. The tap was closed to the syringe. The two open limbs of the tap were flushed with a little of the blood to be sampled, the tap was turned, 2 ml of blood was admitted to the syringe, the tap was closed, and a thin rubber cap was placed over the outer axial limb of the tap (fig. 1B). The syringe was then immersed in a water bath at the same temperature as the animal's nasopharynx and clamped, at an angle of 45°, to a shaft rotating at about 30 rev min^{-1}. Thus the bubble moved to and fro along the syringe, in a helical fashion, with each rotation.

After 2 min the rotation was stopped, the syringe was turned tap uppermost, and the tap was turned to connect the axial limb to the contents of the syringe. As a result, the bubble collected in the conical deadspace and communicated, via a plug of blood, with the rubber cap. A 100-µlitre Hamilton gas-tight syringe was flushed with air to remove any traces of previous samples and its needle was inserted through the cap and the plug of blood into the bubble. A volume of 110 µlitre of gas was drawn up and the plunger was then pushed down to the 100-µlitre mark (fig. 1C). The 100 µlitre of equilibrated gas was then injected quickly into the bottom of a 250-µlitre capacity reservoir tube through which the mass spectrometer (Centronic MGA 200) was sampling room air at about 300 µlitre s^{-1} (fig. 1D). Two Millipore filters in the base of the reservoir tube protected the sampling capillary of the mass spectrometer from accidental blood contamination.

The mass spectrometer was on line to a mini-computer (Data General Nova 2). By cueing a program 1–3 s before injecting the gas the computer was caused to read, by means of its analog-to-digital converters, the relevant five channels of the mass spectrometer at 68 Hz for 9 s, thereby capturing the transient changes in mixture associated with the bubble: nitrogen decreased to a minimum and recovered; carbon dioxide, nitrous oxide, oxygen and halothane increased to a peak and decreased again. The program then determined the height of each base-line and the area of each transient and combined these data with calibration data to perform a complete analysis of the bubble. The details have been published elsewhere (Mapleson, Chilcoat and Willis, 1980); it is sufficient to record here that carbon dioxide was measured at mass 12, nitrogen at 28, nitrous oxide at 30, oxygen at 32 and halothane at 117, with corrections, in the computer, for interfering molecular fragments.

THEORY

The equations governing the exchange of gases between bubble and blood are derived in the Appendix for two conditions: constant bubble volume and constant bubble pressure. Because of the practical problems of working at constant volume the apparatus was designed (see above) to ensure that the bubble pressure was constant to within ±1% and only the equations for constant pressure are considered here.

Equations (2) and (3) in the Appendix were solved first for a set of "standard conditions" (table I) typical of the circumstances in which the technique was to be used, that is measurements on the arterial blood of a dog, in which anaesthesia was being maintained with halothane 1% in 50% nitrous oxide in oxygen. The following conditions were assumed: Pa_{CO_2} normal, Pa_{O_2} such as would occur with a moderately uneven ventilation–perfusion distribution, Pa_{N_2} zero, $Pa_{N_2O} = 90\%$ of PI_{N_2O}.

TABLE I *Partial pressures of gases in a 0.2-ml bubble before (Pg) and after (Pe) equilibration with 2 ml blood with initial gas tensions Pb; Pe calculated according to equations (2) and (3) in the Appendix assuming the differential blood-gas partition coefficients (λ) indicated. Values of λ from Steward, Allott and Mapleson (1975) (halothane), Lunn and Mapleson (1963) (carbon dioxide), Steward and others (1973) (nitrous oxide) and by calculation from the oxygen–haemoglobin dissociation curve for the dog (Rossing and Cain, 1966)*

Gas	λ	Pg (kPa)	Pb (kPa)	Pe (kPa)	$\frac{Pe-Pb}{Pb}$ (%)
Halothane	3.5	0	0.66	0.65	−2.6
Carbon dioxide	4	0	5.32	5.20	−2.3
Nitrous oxide	0.47	47.5	42.75	44.10	+3.1
Oxygen	0.03	47.5	28.50	45.04	+57.9
Total		95.0	77.23	95.0	

It should be noted in table I that the sum of the initial tensions in blood (Pb) is only 77 kPa. Since the sum of the tensions at equilibrium (Pe) is necessarily one dry atmosphere (95 kPa), the tension of at least one gas must increase substantially. In fact the oxygen tension increases more than 50%. Thus, as Nunn (1962) pointed out, the technique is useless for measuring the high oxygen tensions common under anaesthesia. However, the equilibrium partial pressures of halothane, carbon dioxide and nitrous oxide are all within a few per cent of the initial blood tensions.

When the equations were solved for a wide range of conditions it was found that the errors for carbon dioxide and halothane changed by less than ±1% for any one of the following changes (where Pb_x and Pg_x = initial blood tension and initial gas partial pressure of gas x, and λ = differential blood-gas partition coefficient, that is change in concentration in blood divided by change in equilibrium concentration in gas):

(1) Blood volume ±25%.

(2) Initial bubble volume ±25%.

(3) λ for halothane ±25%.

(4) Pb_{CO_2} (initial tension of carbon dioxide) ±2.8 kPa (i.e. λ for carbon dioxide from 3.2 to 6 (Lunn and Mapleson, 1963)).

(5) Pb_{hal} up to at least 5 kPa.

(6) Pb_{O_2} +10, −15 kPa (i.e. down to 97% saturation (Rossing and Cain, 1966), below which the bubble volume decreases during equilibration to less than 0.15 ml).

(7) $Pb_{N_2O}/Pg_{N_2O} = 1.2$–$0.5$ (approximately equivalent, with the specified technique, to $Pa_{N_2O}/PI_{N_2O} = 1.2$–$0.5$).

(8) Gas entering vaporizer (from which gas the bubble is drawn) 25–75% nitrous oxide, but Pb_{N_2O}/Pg_{N_2O} constant at 0.9.

Thus the results for carbon dioxide and halothane are very insensitive to the variables in the procedure including errors in the estimated values of λ.

The error in nitrous oxide was more variable (because of its lower solubility in blood) especially in response to changes in Pb_{N_2O}/Pg_{N_2O}. However, when correction to the equilibrated partial pressure Pe was made for the exchange of nitrous oxide between bubble and blood, using equation (5) in the Appendix, the total error in estimating the initial blood tension of nitrous oxide lay between −2% and +5% for any one of the above changes of circumstance.

Thus, according to theory, the method should work well over a wide range of conditions for carbon dioxide, halothane and any other gas with similarly large blood-gas partition coefficient. In man, with λ = 2.4 for halothane (Steward et al., 1973) instead of 3.5 (Steward, Allott and Mapleson, 1975), the systematic error under "standard conditions" is 3.8%. It should also work well for nitrous oxide and agents of similar solubility, provided that correction is made for gas exchange or that the blood is nearly in equilibrium with the gas at the start.

EXPERIMENTAL TESTS OF THE TECHNIQUE

For experimental testing of the technique about 30 ml of blood from a dog, normally an Alsatian, was equilibrated for at least 30 min at 37 °C in a bubble-through tonometer (fig. 2) with a humidified gas mixture containing about 1% halothane and 5% carbon dioxide in Entonox (50% nitrous oxide in oxygen). Periodically, a sample of the blood was drawn for equilibration with a bubble of Entonox. The procedure was as follows.

Sample syringe flushed with Entonox at port A (fig. 2); gas flow diverted through port B and a resistance such that the pressure in the Fluotec vaporizer was unaltered; sample syringe connected as shown in figure 2; three-way tap on the sample syringe flushed with blood by means of the flushing syringe; 2 ml of blood drawn into the sample syringe; flushing blood and gas flow restored to the bubble tonometer.

The blood and bubble in the sample syringe were then equilibrated as described in "Technique" above (except that equilibration times longer than 2 min were used sometimes) and the results of the analysis of the equilibrated bubble were compared with conventional, continuous-flow, analyses of the gas mixture perfusing the bulk blood. These analyses were made by connecting the mass spectrometer sampling probe to port B for much of the duration of the experiment. In making the comparison, correction was made for any differences in sensitivity between the discrete-sample and continuous-flow modes of operation of the mass spectrometer (Mapleson, Chilcoat and Willis, 1980). These differences were determined periodically by using both modes to measure the perfusing gas mixture or a similar mixture stored in an 11-litre glass jar.

In two experiments a rotating tonometer was immersed in the same water bath as the bubble tonometer and the same equilibrating gas mixture was caused to flow through both. The rotating tonometer was cylindrical and was rotated about its horizontal axis to spread the blood to a thin film. There was free egress of gas from the rotating tonometer so that the equilibration therein was undoubtedly at atmospheric pressure, whereas the pressure in the bubbles must have been marginally in excess of atmospheric. Samples were taken alternately from the two tonometers.

EXPERIMENTAL RESULTS

Initial experimental tests seemed to indicate that the technique was giving results in accord with theory after equilibration for 2 min. In use however, it became evident that the technique was underestimating blood tensions of carbon dioxide and halothane to a variable degree. It seemed that the possible causes were:

(1) Equilibration may in fact take longer than 2 min. This was tested very thoroughly and shown not to be true (see table II below).

(2) The tensions in the blood from the bubble tonometer (fig. 2) which was used for the great majority of the tests may be greater than assumed because the total pressure in the bubbles is greater

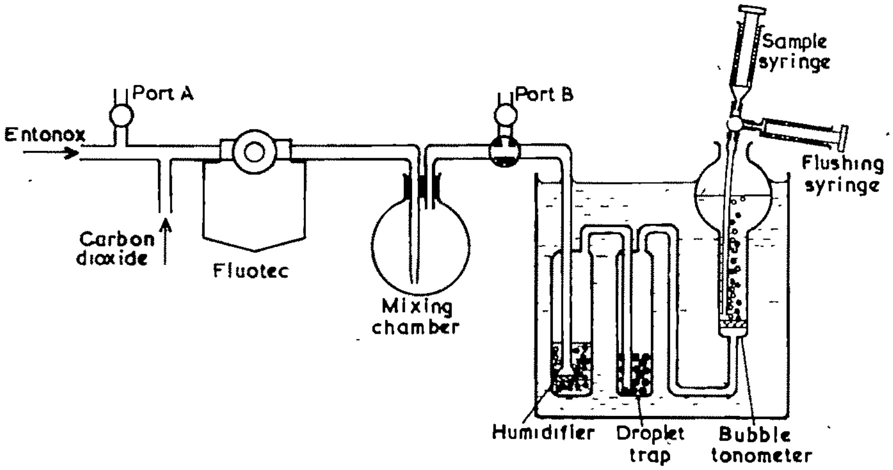

FIG. 2. Apparatus for the bulk equilibration of blood to provide samples with known tensions.

than atmospheric. However, the mean hydrostatic pressure in the blood was less than 1% of an atmosphere and surface tension can be calculated to cause an excess of only about 1% for bubbles of radius 0.1 mm (smaller than the bubbles appeared to be). Experimental comparison of samples from the bubble and rotating tonometers showed that, for a total of nine samples from each, the mean difference in measured tension of carbon dioxide (bubble minus rotating tonometer) was −1.1%±3.4% (95% confidence limits) and of halothane was +1.2%±1.3%. Therefore any excess of tension in samples from the bubble tonometer is almost certainly less than 2%.

(3) The requirement of the theory that the total pressure of the bubble be constant during equilibration may not have been met. However, vertical movement of the bubble during rotation accounted for a pressure variation of less than ±0.2%, and any difference between the pressure of the nitrous oxide–oxygen gas on initial flushing of the syringe and the pressure of the bubble during equilibration was simply equivalent to a change in initial bubble volume (to which the results are insensitive—see "Theory" above). During part of the time spent in sampling the bubble, the pressure was about 1.5 kPa less than during equilibration; therefore all component gases must have begun to evolve from the blood. However, the then unfavourable conditions for equilibration would limit the change in concentration of any component gas to much less than 1.5% of its equilibrated value.

(4) In order to introduce the tip of the needle of the 100-μlitre syringe into the bubble it was necessary to hold the syringe (out of the water bath) against a light, but the 5-ml syringe (with the then connected 100-μlitre syringe) was returned to the water before drawing the bubble sample. Thus there must have been some small reduction in the temperature of the blood and bubble leading to preferential resolution of halothane and carbon dioxide because of the high temperature coefficient of the solubility in blood of the former (Allott et al., 1973) and the marked temperature-dependence of the carbon dioxide dissociation curve (Kelman and Nunn, 1968). However, the brevity of the removal from the bath (about 30 s) and the unfavourable conditions for equilibration can be expected to limit the effect. That the effect was indeed small is shown by table III below.

(5) If a trace of blood enters the 100-μlitre syringe it will cool very rapidly to room temperature, the solubility of carbon dioxide and halothane in the blood will increase and their tensions will decrease. Therefore, carbon dioxide and halothane will be lost from the gas to this blood before the gas enters the mass spectrometer. With skill and care this effect was minimized but, even though a sample was rejected if blood was visible in the 100-μlitre syringe, traces of blood were sometimes found on the inside of the reservoir tube (fig. 1D) and on the Millipore filters. That this was indeed a cause of systematic error is shown by the following observations. Deliberate contamination of the reservoir tube on one occasion between two series of injections of dry gas from a dry syringe produced an immediate 5% decrease in the sensitivity to carbon dioxide in the samples. On many occasions, injection of dry gas immediately after gas from a bubble (and using the same 100-μlitre syringe so that it was subject to similar blood contamination) gave measurements that, for both carbon dioxide and halothane, were up to 8% lower than injections of the same dry gas from a different, dry syringe.

(6) If a trace of oil or grease contaminates the 100-μlitre syringe, reservoir tube, filter or sampling capillary then (because of the very high solubility of halothane in oils) halothane will be lost from the samples. The fact that sensitivity to halothane in discrete samples changed occasionally when there was little change in sensitivity to carbon dioxide is evidence presumably that this occurred sometimes even though oil contamination was never detected visually.

Once it had been established that the main cause of error was blood contamination with occasional trouble from oil contamination, it was possible to analyse rationally the results of all the test experiments.

In table II the effect of blood and oil contamination was eliminated largely by comparing pairs

TABLE II. *Effect of different equilibration times. Pooled results of four experiments* (n = *21*)

	Partial pressure in bubble after 4 min equilibration minus partial pressure after 2 min, as % of former	
	Mean	95% Confidence limits
Carbon dioxide	−0.1%	−1.1 to +1.0%
Halothane	0.8%	−0.4 to +2.0%

of results, one member of each pair after equilibration for 2 min the other after equilibration for 4 min, where the two members came in quick succession and therefore were likely to be subject to similar errors. The table shows that any further equilibration between bubble and blood in the interval from 2 min to 4 min is not statistically significant and probably less than 1 or 2%. Since the equilibration process is probably roughly exponential, any further equilibration after 4 min must be trivial. Therefore, after 2 min, equilibration is probably at least 98 or 99% complete.

In table III the effect of blood and oil contamination is minimized by considering only those bubble samples the injection of which was immediately followed by the injection of a sample of dry gas (using the same 100-µlitre syringe, and therefore subject to similar contamination) to determine the discrete-sample sensitivity at that moment. The table shows that, for halothane, the ratio of gas partial pressure after equilibration to blood tension before, was in very close agreement with theory; for carbon dioxide it was 2–3% lower.

TABLE III. *Comparison of experimental* (R_E) *and theoretical* (R_T) *ratios of bubble partial pressure (after equilibration) to blood tension (before equilibration). Pooled results of five experiments* (n = *94*) *using results only where the discrete-sample sensitivity had been determined immediately after analysing the equilibrated bubble, using the same 100-µlitre syringe and hence subject to approximately the same blood contamination. In calculating* R_E *it was assumed that the blood tension before equilibration was equal to the partial pressure in the gas perfusing the blood in the tonometer in figure 2, and, where equilibration was for only 2 min* (n = *54*), *the halothane result was increased by 0.8% to compensate for the most probable incompleteness of equilibration shown in table II.* R_T *was calculated for the conditions of each experiment*

	R_E/R_T	
	Mean	95% Confidence limits of the mean
Carbon dioxide	97.5%	96.9–98.1%
Halothane	100.0%	99.5–100.6%

Table IV shows the performance to be expected in practice for various possible regimes of determining the discrete-sample sensitivity. The systematic errors (the shortfall of the figures in the first column below 100%) include the expected difference between bubble partial pressure after equilibration and blood tension before as well as the mean effects of blood and oil contamination and any other systematic errors. If these were corrected on an empirical basis there would remain the random errors in the other columns.

If the discrete-sample sensitivity is determined only at the start of the experiment (but as the mean of several repeat determinations) SD between experiments is about 4% and SD within experiments is about 3%, giving a "total" SD for a single observation in a single experiment of about 5%.

If sensitivity is determined at start and finish with linear interpolation over the time between (typically 3 h), SD between experiments is reduced to 3% and the total SD to 4%.

If sensitivity is determined by a dry gas injection after every sample (using the same 100-µlitre syringe) SD between experiments is less than 2%, but SD within is increased because each determination of sensitivity is then based on a single injection instead of on the mean of several. As a result total SD is again 4%.

Thus, if relative accuracy within an experiment is important, it is best to determine sensitivity before, and perhaps after, the experiment; if accuracy between experiments is more important it is better to determine sensitivity after each sample using the same 100-µlitre syringe.

The technique has been used to measure arterial tensions of carbon dioxide and halothane in dogs anaesthetized with halothane and nitrous oxide (Mapleson et al., 1980) using only a pre-anaesthetic determination of discrete-sample sensitivity. End-tidal partial pressures were monitored also by the same mass spectrometer as used for the discrete samples so that some idea of performance *in vivo* could be obtained by examining the ratios of arterial tension to end-tidal partial pressure ($Pa/P\text{E}'$). After eliminating four rogues (according to the criteria given in the footnote to table IV) from 58 determinations in seven dogs, the pooled within-animal SD for carbon dioxide and halothane was 6% and the between-animal SD was 7%. These results are consistent with the within-experiment and between-experiment SD of about 3% and 4% in the first pair of lines in table IV when allowance is made for the following: errors in end-tidal tension measurement, genuine variation in $Pa/P\text{E}'$, and the fact that blood and oil contamination probably had a greater effect because, only in the last of these animal experiments, was the sampling capillary protected by Millipore filters (fig. 1D).

The *in vitro* tests gave unduly favourable results for nitrous oxide because the initial partial pres-

TABLE IV. *Performance of the technique in practice: experimental ratio (R_E) of bubble partial pressure (after equilibration) to blood tension (before equilibration) for various frequencies of determining the discrete-sample sensitivity. Results, for which equilibration lasted 2 min only, drawn from five experiments.* n = *49 after eliminating five "rogue" results, where a rogue is defined as an injection in which one or more of the following criteria are met: minimum partial pressure of nitrogen during injection "peak" increased by ≥10% of an atmosphere; percentage of air in discrete sample increased by ≥15%, time constant of decay of peak increased by ≥40 ms. The first two criteria are related to air contamination of the bubble which, if it occurs before or during equilibration, gives false results (see text). The third criterion is empirical but is probably related to a "bad" injection or partial occlusion of the mass-spectrometer sampling capillary by traces of blood. The necessary data for assessment are amongst the diagnostics printed, along with the results, for each injection.* *$\sqrt{(SD^2 \text{ within} + SD^2 \text{ between})}$

	Mean R_E (%)	SD between experiments (%)	SD within experiments (%)	"Total" SD* for single observation in single experiment (%)
Discrete-sample sensitivity determined at:				
Start of experiment only				
Carbon dioxide	91.0	3.8	3.3	5.0
Halothane	93.7	3.7	2.8	4.6
Start and finish				
Carbon dioxide	91.5	3.1	3.4	4.6
Halothane	93.1	2.6	2.7	3.8
After each bubble injection using same 100-μlitre syringe				
Carbon dioxide	94.3	1.5	4.3	4.6
Halothane	95.0	0.3	3.0	3.0

sures of nitrous oxide and oxygen in the bubble were very close to the initial tensions in the blood. In the *in vivo* use of the method, although the end-tidal partial pressure of nitrous oxide and hence its arterial tension was always close to the inspired partial pressure ($P\mathrm{E}'_{\mathrm{N_2O}} = 0.95$ to $1.06\ P\mathrm{I}_{\mathrm{N_2O}}$), the arterial oxygen tension (as measured by a conventional blood-gas electrode) was usually well below the inspired partial pressure of oxygen ($P\mathrm{a}_{\mathrm{O_2}} = 0.5$ to $0.8\ P\mathrm{I}_{\mathrm{O_2}}$). Since the initial partial pressures of nitrous oxide and oxygen in the bubble are almost the same as their inspired partial pressures, it follows that $P\mathrm{a}/P\mathrm{E}'$ ratios for nitrous oxide provide some indication of the *in vivo* performance of the technique for this gas. Even without correcting for nitrous oxide exchange between bubble and blood (see "Theory" above) the pooled within-animal SD was 1.7% and the between-animal SD was 2.3% giving a total SD of 2.9%.

DISCUSSION

Previous investigators have equilibrated bubble and blood for 5–7 min. Therefore it was a pleasant surprise to find that, for carbon dioxide and halothane, equilibration was virtually complete in only 2 min. However, it is notable that the only previous direct comparisons of different equilibration times are those of Krogh (1908), who showed that equilibration of 3–5 μlitre of gas with 1–2 ml of water was complete in 2 min but not in 1 min and that, on equilibrating venous blood at 1 °C, the results at 5 min were the same as at 8 min.

Since the main cause of error in the present method is believed to be blood and oil contamination, it is important, as in the present study, to change the Millipore filters as soon as they become contaminated and to rinse the 100-μlitre syringe after each bubble injection. It is possible that errors might be reduced if, in addition, meticulous attention were paid to cleanliness in general, and if the reservoir tube were cleaned after every sample and perhaps if the needle of the 100-μlitre syringe were siliconized in an attempt to prevent blood wetting the needle.

The present bubble size was chosen because it was thought that 100 μlitre would be the minimum to give adequate precision of analysis. However, SD of the analysis of 100-μlitre samples of a mixture of halothane 1% and carbon dioxide 5% in Entonox was generally 1% or less, of each component (Mapleson, Chilcoat and Willis, 1980). Therefore a smaller bubble could be used. This would result in smaller changes in blood tensions during the equilibration (which would reduce the need for correction of nitrous oxide results), but it would probably increase blood-contamination errors. Conversely, contamination errors might be decreased by using an even larger bubble, if necessary with mathematical correction for exchange of all the gases; but this approach would be limited by the between-subject variation of the various blood-gas partition coefficients.

Some of the techniques used by previous workers to transfer the bubble from the equilibration apparatus to the analysis apparatus seem less prone to blood contamination, but the reproducibilities of their results are about the same as ours. Thus Riley, Proemmel and Franke (1945), Shepard and Meier (1957) and Strang (1961) all found SD of about 5% for carbon dioxide, the same as in the present method. Perhaps this is because of greater errors in analysis: the first two studies used chemical absorption and Strang, although using a mass spectrometer, relied on measuring peak deflections on a pen recorder. In terms of nitrous oxide the present, between-animal SD of $Pa/P\text{E}'$ of 2.3% is smaller than the 3.2% of Flook's (1968) gas chromatographic method and, if allowance is made for genuine variation in $Pa/P\text{E}'$, the present, within-animal SD of $Pa/P\text{E}'$ of 1.7% is probably compatible with the 0.9% SD reported by Bowes (1964) for the ratios of measured to known tensions when he tested his gas chromatographic method on 24 consecutive *in vitro* samples of blood equilibrated with known gas mixtures.

In the circumstances for which the technique was designed, the blood, and therefore the bubble, should contain no nitrogen gas. Therefore the computer was programmed to interpret any nitrogen in its analysis of the bubble as a result of air contamination which was then mathematically "removed" from the sample. By this means several sources of error were corrected: genuine air contamination of the bubble after equilibration (perhaps from leaks in the 100-μlitre syringe), variations in the volume of gas injected (a volume of more than 100-μlitre appears as "negative" air contamination) and variation in carrier-gas flow (which the program could not distinguish from changes in injected volume). This procedure helped considerably in reducing random errors in the analysis of the bubble, but it had a disadvantage: if the bubble became contaminated with air *before* equilibration (perhaps by leakage in the equilibration syringe) this made little difference to the partial pressures of carbon dioxide and halothane in the bubble at the end of the equilibration; therefore, when the air was mathematically removed from the bubble, the carbon dioxide and halothane partial pressures were increased to falsely high values. However, when air contamination of this kind became serious, one of the criteria (see legend to table IV) of a rogue result was satisfied and it could be rejected. (Rogues accounted for less than 10% of the results in both the *in vitro* tests and in the live-animal experiments.)

If the technique were required to measure the tension of nitrogen in blood (a difficult requirement because of its low solubility) the correction for apparent air contamination could not be used and random errors generally would be increased unless a foreign gas, such as argon, were used as the carrier gas. This has computational advantages (Mapleson, Chilcoat and Willis, 1980) but is less convenient experimentally.

If the technique is ever to be extended to oxygen at high tensions, or even at low tensions if the sum of the blood-gas tensions is appreciably less than one dry atmosphere (as a result of ventilation–perfusion mismatch or as in venous blood), then it would probably be essential to use the technically more difficult constant-volume technique (see "Theory"). Strangely, although the originator of the method (Krogh, 1908) achieved success with that technique (at normal oxygen tensions) no-one since seems to have tried it.

The method provides a fairly rapid means of determining the tensions of inhaled anaesthetics and carbon dioxide in 2-ml samples of blood. The method is convenient if a multi-channel mass spectrometer is already being used for respiratory monitoring. The necessary computing power can now be bought for a small fraction of the cost of the mass spectrometer.

APPENDIX

Let a volume of blood $V\text{b}$, containing dissolved gases at tensions $P\text{b}_i$ ($i = 1$ to n), be equilibrated with a bubble of gas, initially of volume Vg_0, at total pressure Pg_0, and containing gases whose partial pressures are Pg_i. When equilibration is complete, let the blood-gas tensions and the gas partial pressures be Pe_i, and the gas volume be Vg_e at a total pressure Pg_e. Let the differential blood/gas partition coefficients (change in concentration in blood divided by change in equilibrium concentration in gas) be λ_i between the tensions Pb_i and Pe_i. (Note that this does not imply a linear concentration–tension relationship between Pb_i and Pe_i.)

Then, for each gas, neglecting metabolism, total quantity at equilibrium = total quantity at start:

$$(Vg_e+\lambda_i Vb)Pe_i = Vg_0 Pg_i+\lambda_i Vb\, Pb_i \tag{1}$$

Solving for Pe_i yields

$$Pe_i = \frac{Vg_0 Pg_i+\lambda_i Vb Pb_i}{Vg_e+\lambda_i Vb} \tag{2}$$

Condition I: Constant bubble volume

If the equilibration is performed at constant bubble volume ($Vg_e = Vg_0$) then Pe_i, the equilibrium partial pressure for each gas is determined by (2) independently of the other gases.

Condition II. Constant bubble pressure

If the equilibration is performed at constant bubble pressure ($Pg_e = Pg_0$) then $Vg_e \neq Vg_0$ but

$$\Sigma Pe_i = \Sigma Pg_i (= Pg_0) \tag{3}$$

Therefore Pe_i, the equilibrium partial pressure for each gas, depends on Vg_e which, in turn, depends on the way in which all the gases equilibrate. However, the n equations (2), together with equation (3), can be solved for the n values of Pe_i and for Vg_e. A numerical solution may be obtained iteratively as follows.

(1) Solve the n equations (2) with an estimate of Vg_e (initially Vg_0) to obtain a set of Pe_i (i.e. equilibrate at constant volume)

(2) Calculate an improved estimate of Vg_e equal to the old estimate $\times\, \Sigma Pe_i/Pg_0$ (i.e. restore the pressure of the bubble to its original value).

(3) Repeat steps 1 and 2 until the changes from one iteration to the next are acceptably small.

A program to handle these calculations for a mixture of five gases can just be fitted into a Texas Instruments TI58 programmable pocket calculator. Since λ for oxygen is sharply dependent on the range of tensions through which the blood passes in the equilibration process, it is necessary to run the program once with an approximate value for λO_2, that is to perform a "trial equilibration", in order to obtain an estimate of the tension range involved and hence a good estimate of λO_2 for a second run, that is a "definitive equilibration". The program can then be used to reveal how closely the calculated values of Pe_i come to the assumed values of Pb_i for any given circumstances.

For any circumstances encountered experimentally in which the calculated discrepancy between Pe_i and Pb_i is unacceptable, it may be practicable to apply a theoretical correction to the measured value of Pe_i as follows. Solving (1) for Pb_i yields:

$$Pb_i = Pe_i+\frac{(Vg_e-Vg_0)Pe_i+Vg_0(Pe_i-Pg_i)}{\lambda_i Vb} \tag{4}$$

It is not difficult experimentally to keep Vg_0, Vb and Pg_i close to known values. Therefore, if Vg_e can be measured, equation (4) may be solved to give an improved estimate of Pb_i for any gas for which λ_i is known. This largely excludes oxygen because, even if a full specification of the dissociation curve were included in the calculation, its parameters include pH and 2–3 DPG which would need to be known.

If Vg_e cannot be measured, as in the experimental technique described in the main part of the paper, but the gas exchange between bubble and blood can be attributed mainly to one component, the jth, then

$$Vg_e - Vg_0 \simeq Vg_e Pe_j - Vg_0 Pg_j$$

Solving for Vg_e and substituting in (4) yields

$$Pb_i \simeq Pe_i + \frac{Vg_0}{\lambda_i Vb}\left\{Pe_i\frac{1-Pg_j}{1-Pe_j} - Pg_i\right\} \tag{5}$$

ACKNOWLEDGEMENT

This work was supported by a grant from the Medical Research Council.

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EVALUATION DE LA TENSION GAZ-SANG DANS L'ANESTHESIE PAR EQUILIBRATION DE BULLE ET SPECTROMETRIE DE MASSE

RESUME

Si l'on équilibre un petite bulle de gaz avec une quantité de sang, les pressions partielles des composantes de la bulle après l'équilibration s'approchent des tensions primaires du sang. On décrit une méthode selon laquelle on analyse la bulle au moyen d'un spectromètre de masse respiratoire branché à un mini-ordinateur. La fonction normale de surveillance de la respiration du spectromètre de masse ne doit être interrompue que pendant 20 s pour chaque échantillon et le procédé total d'equilibration et d'analyse ne demande que 3 min. D'après les études théoriques, les essais expérimentaux et les enregistrements relatifs à une utilisation expérimentale, on voit que l'on peut mesurer chez un sujet anesthésié à l'halothane dans du protoxyde d'azote et oxygène, les tensions avec une SD globale de 5% pour l'anhydride carbonique et l'halothane, et, sous certaines réserves, avec une SD d'environ 3% pour le protoxyde d'azote.

BLUTGASDRUCKMESSUNGEN BEI DER NARKOSE MITTELS GASBLASENEQUILIBRATION UND MASSENSPEKTROMETRIE

ZUSAMMENFASSUNG

Wenn eine kleine Gasblase mit einem Blutvolumen ins Gleichgewicht gebracht wird, gleichen die Teildrücke der Komponente der Blase nach der Equilibration ungefähr den ursprunglichen Drücken im Blut. Es wird eine Methode beschrieben, bei der die Blase mittels eines an einen Kleincomputer angeschlossenen Atmungsmassenspektrometers analysiert wird. Die normale atmungsuberwachende Funktion des Massenspektrometers braucht bei jeder Probe nur 20 Sekunden lang unterbrochen zu werden und das vollstandige Equilibrations- und Analyse-Verfahren dauert nur 3 Minuten. Theoretische Studien, experimentelle Versuche und Aufzeichnugen von experimentellen Anwendungen zeigen, dass bei einem mit Halothan in Stickstoffoxydul und Sauerstoff narkotisierten Patienten die Drucke mit einer durchschnittlichen Standardabweichung von 5% fur Kohlensaure und Halothan und—vorbehaltlich—einer Standardabweichung von ca. 3% für Stickstoffoxydul gemessen werden konnen.

MEDICION DE LA TENSION GAS-SANGRE EN LA ANESTESIA POR EQUIPARAMIENTO DE BURBUJA Y ESPECTROMETRIA DE MASA

SUMARIO

Si se equipara a una pequeña búrbuja de gas con un volumen de sangre, las presiones parciales de los componentes de la búrbuja después del equiparamiento se aproximan a las tensiones originales de la sangre. Se describe un método según el cual se analiza la búrbuja mediante un espectrómetro de masa respiratoria conectado a una mini-computadora. No se necesita interrumpir màs de 20 s para cada muestra a la función de control respiratorio normal y el procedimiento de equiparamiento y de análisis en total toma sólo 3 min Los estudios teóricos, los ensayos experimentales y los registros del uso experimental indican que, en un paciente anestesiado con halotano en óxido nitroso y oxígeno, se pueden medir las tensiones con una SD global de un 5% para el anhídrido carbónico y el halotano, y con algunas reservas, una SD de cerca del 3% para el óxido nitroso.

Br. J. Anaesth. (1980), **52**, 1071

EFFECTS OF SUBARACHNOID SPINAL NERVE BLOCK AND ARTERIAL $P\text{CO}_2$ ON COLON BLOOD FLOW IN THE DOG

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SUMMARY

Changes in colon blood flow in greyhounds were measured in response to acute changes in arterial $P\text{CO}_2$, before and after spinal nerve block. Colon blood flow increased significantly after spinal nerve block, irrespective of $P\text{CO}_2$. The findings may be of clinical importance in man

Surgery of the colon carries a high frequency of serious complications. The frequency of dehiscence after a colon anastomosis may be as great as 69% (Goligher, Graham and De Dombal, 1970). The mortality rate among patients whose anastomosis has broken down is about 35% in most series (Irvin and Goligher, 1973; Schrock, Deveney and Dunphy, 1973; Aitkenhead, Wishart and Peebles Brown, 1978), and morbidity is considerable also.

A number of factors are known to influence anastomotic dehiscence in the colon, including several which may reduce oxygen availability: the amount of blood transfused at operation or in the 24 h following surgery (Whitaker, Dixon and Greatorex, 1970; Schrock, Deveney and Dunphy, 1973), hypotension during surgery, or a preoperative haematocrit of less than 35%. In experimental animals wound healing is adversely affected by remote trauma, hypovolaemia and hypoxia (Zederfeldt, 1957; Stephens and Hunt, 1971; Hunt and Pai, 1972). It has been demonstrated in dogs that hypovolaemia produces a marked reduction in colon blood flow (Whitaker, Dixon and Greatorex, 1970; Gilmour et al., 1980). The importance of blood supply to colon anastomoses has been emphasized in a review by Everett (1974). A clinical study (Aitkenhead, Wishart and Peebles Brown, 1978) has suggested that colon anastomoses performed under spinal nerve block may have a smaller frequency of breakdown than anastomoses constructed during conventional general anaesthesia.

We have investigated the effects of spinal nerve block on colon blood flow in an animal model. There were two experiments: (A) into the effects on colon blood flow of subarachnoid spinal nerve block; (B) into the effects on colon blood flow of changes in arterial carbon dioxide tension before and after subarachnoid spinal nerve block.

The animal model and measurement techniques are described fully elsewhere (Gilmour et al., 1980), but are outlined here.

METHODS

Adult greyhounds weighing between 19 and 35 kg were anaesthetized using pentobarbitone 40 mg kg^{-1}. After endotracheal intubation, muscle relaxation was achieved using pancuronium 0.1 mg kg^{-1} and intermittent positive pressure ventilation was instituted using a Palmer pump supplied with oxygen-enriched air. Minute volume and inspired oxygen concentration were adjusted to give arterial $P\text{CO}_2$ 4.7–6.0 kPa and an arterial $P\text{O}_2$ 12–16 kPa. E.c.g. was recorded using needle electrodes placed under the skin of each limb. Polyethylene catheters were placed with their tips in the right atrium and descending aorta via the left femoral vein and artery respectively. A Swan–Ganz catheter was placed in the left external jugular vein and advanced under x-ray control until its tip lay in the main pulmonary artery. E.c.g., systemic and pulmonary arterial pressures and right atrial pressure were recorded using an eight-channel Mingograf recorder. Cardiac output was measured by the thermal dilution technique using the Swan-Ganz catheter and a cardiac output computer (Type 3750, Cardiovascular Instruments). Core temperature was measured using a thermocouple temperature probe positioned in the oesophagus.

The abdomen was opened through a midline incision, and splenectomy performed. This pro-

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0007–0912/80/111071–07 $01.00

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cedure in the dog is known to produce a model which more closely simulates the human cardiovascular response to stress (Chien et al., 1973). A number-4 Cournand cardiac catheter was introduced into the right femoral artery and manoeuvred under x-ray control until its tip lay in the cranial mesenteric artery just proximal to the common colic artery. The position was confirmed under x-ray control by the injection of a small volume of meglumine iothalamate 60% (Conray 280). A 20-gauge Teflon cannula was introduced through a small vein draining the colon and advanced until its tip lay in the left colic vein. This cannula was connected to an extension catheter and used for sampling colon venous blood. The colon was then approximated to the abdominal wall in a natural position to the left of the midline using two silk sutures 3 cm apart. The small bowel was packed to the right side of the abdomen which was then closed with through-and-through silk sutures.

A suitably collimated scintillation counter was positioned over the dog at an angle of 45° in such a way that it pointed directly at the loop of colon, with the small bowel lying outside its field of uptake. Colon blood flow measurements were made by injecting xenon-133 500 µCi followed by 4 ml of normal saline through the mesenteric artery catheter. The washout of xenon-133 from the colon was recorded using a ratemeter and potentiometric recorder and the colon blood flow calculated from the washout curve according to the formula of Kety (1960). We had determined previously the value in this equation of the tissue/blood partition coefficient for xenon-133 in the colon.

Measurements of $P\text{O}_2$, $P\text{CO}_2$ and pH were made on samples of arterial, right atrial and colon venous blood using an IL 213 blood-gas analyser, and the values corrected for temperature where appropriate. Haemoglobin was estimated on the arterial sample using an IL 182 co-oximeter.

Experiment A

The effects of subarachnoid spinal nerve block were studied in 30 dogs. Blood samples were analysed, arterial pressures, heart rate, cardiac output and colon blood flow were measured and the oxygen consumption and vascular resistance of the colon were calculated. A 20-gauge needle was introduced at the interspace of the 6th and 7th lumbar vertebrae or the lumbosacral junction into the subarachnoid space. Because of the very small interlaminar space and the lax dura mater in the dog, this procedure was carried out under radiographic control. Bupivacaine was injected into the subarachnoid space using a dose of 0.2 ml kg^{-1} of 0.5% solution. Twenty minutes later all measurements were repeated.

Experiment B

The effects of changes in arterial $P\text{CO}_2$ before and after spinal nerve block were studied in 12 of the dogs. After adequate time for stabilization, measurements were performed at 15-min intervals throughout the experiment. After two control groups of measurements, acute hypocapnia to an arterial $P\text{CO}_2$ between 2.1 and 3.1 kPa was induced, by doubling the inspired minute volume, and the measurements were repeated. Arterial $P\text{CO}_2$ was then restored to normal and two further groups of control measurements made. Acute hypercapnia was induced by the addition of carbon dioxide to the inspired gas mixture to produce arterial $P\text{CO}_2$ between 10.0 and 12.5 kPa, and the measurements were repeated. Arterial $P\text{CO}_2$ was once again restored to normal and two final groups of control measurements were performed. Subarachnoid spinal nerve block was then undertaken as in experiment A and, after 20 min, all measurements and $P\text{CO}_2$ changes undertaken before spinal nerve block were repeated.

Statistics

Values were analysed using paired Student's *t* test.

RESULTS

Experiment A (table I)

Subarachnoid spinal nerve block produced a decrease in mean arterial pressure and in heart rate. Total peripheral resistance decreased by 31.5%. Colon blood flow increased by 22.3%, and there was a decrease of 43.9% in colon vascular resistance. There was a significant decrease in the difference between oxygen tension in arterial and colon venous blood after the block, and this was reflected in the oxygen content differences. Spinal nerve block was associated with a significant decrease in colon oxygen consumption.

Experiment B

Hypocapnia (table II). Hypocapnia produced a modest decrease in arterial pressure both before and after spinal nerve block, but there was no change in heart rate. Colon blood flow was reduced by 19.3% in response to hypocapnia before the

TABLE I. *Effects of spinal nerve block. Values from 30 dogs expressed as mean (SEM)*

	Before block	*P*	Block
Colon blood flow (ml min^{-1} per 100 g)	36.7 (1.0)	<0.001	44.9 (1.6)
Colon vascular resistance (units)	3.92 (0.13)	<0.0001	2.20 (0.09)
Colon oxygen consumption (ml min^{-1} per 100 g)	1.33 (0.09)	<0.01	1.10 (0.08)
Mean arterial pressure (mm Hg)	140.7 (2.4)	<0.0001	96.5 (3.6)
Heart rate (beat min^{-1})	152.9 (5.0)	<0.0001	132.4 (5.6)
Total peripheral resistance (units)	44.2 (2.3)	<0.0001	30.3 (1.7)
Arterial oxygen tension (kPa)	15.6 (0.4)	n.s.	15.5 (0.4)
Colon venous oxygen tension (kPa)	7.7 (0.2)	<0.001	8.5 (0.3)
Arterial oxygen content (ml dl^{-1})	24.55 (0.75)	n.s.	24.39 (0.86)
Colon venous oxygen content (ml dl^{-1})	21.15 (0.86)	<0.01	22.07 (0.95)

TABLE II. *Effects of hypocapnia and spinal nerve block. Values from 12 dogs expressed as mean (SEM)*

	Before block			Block		
	Control	*P*	Hypocapnia	Control	*P*	Hypocapnia
Colon blood flow (ml min^{-1} per 100 g)	41.0 (1.5)	<0.0005	33.1 (1.5)	47.3 (1.5)	<0.0001	33.1 (1.6)
Colon vascular resistance (units)	3.36 (0.17)	<0.005	3.91 (0.26)	2.07 (0.08)	<0.0005	2.75 (0.11)
Mean arterial pressure (mm Hg)	135.8 (4.3)	<0.005	126.0 (5.5)	97.3 (4.1)	<0.01	90.2 (4.3)
Total peripheral resistance (units)	32.4 (3.6)	n.s.	29.5 (3.4)	28.0 (2.6)	n.s.	25.1 (2.8)

TABLE III. *Effects of hypercapnia and spinal nerve block. Values from 12 dogs expressed as mean (SEM)*

	Before block			Block		
	Control	*P*	Hypercapnia	Control	*P*	Hypercapnia
Colon blood flow (ml min^{-1} per 100 g)	40.5 (1.5)	<0.0005	57.4 (3.4)	45.3 (1.7)	<0.0001	62.6 (2.2)
Colon vascular resistance (units)	3.53 (0.17)	<0.0001	2.44 (0.13)	2.24 (0.09)	<0.0001	1.14 (0.08)
Mean arterial pressure (mm Hg)	140.8 (4.0)	n.s.	135.8 (4.9)	101.5 (5.3)	<0.0001	70.2 (4.3)
Total peripheral resistance (units)	34.8 (2.3)	n.s.	28.8 (2.5)	28.0 (2.0)	<0.0005	17.6 (1.7)

block, and by 30.0% after the block, and there were 16.4% and 32.9% increases in colon vascular resistance before and after the block respectively. There was no significant change in total peripheral resistance in response to hypocapnia, irrespective of spinal nerve block. Hypocapnia produced no significant changes in colon oxygen consumption or arterial–venous oxygen tension or content differences.

Hypercapnia (table III). There was no significant alteration in arterial pressure in response to hypercapnia before spinal nerve block, but after the block, increasing the $P\text{CO}_2$ resulted in a 30.9% decrease in mean arterial pressure, and a 37.1% decrease in total peripheral resistance. Hypercapnia was associated with a 41.7% increase in colon blood flow and a 30.9% decrease in colon vascular resistance before spinal nerve block, and a 38.2% increase in colon blood flow and a 49.1% decrease in colon vascular resistance after the block.

Colon oxygen consumption and arterial–venous oxygen tension and content differences were not significantly altered by hypercapnia. Figure 1 shows the relationship between colon blood flow and arterial $P\text{CO}_2$ before and after spinal nerve block. There was a good correlation coefficient for both regression lines, and it can be seen that,

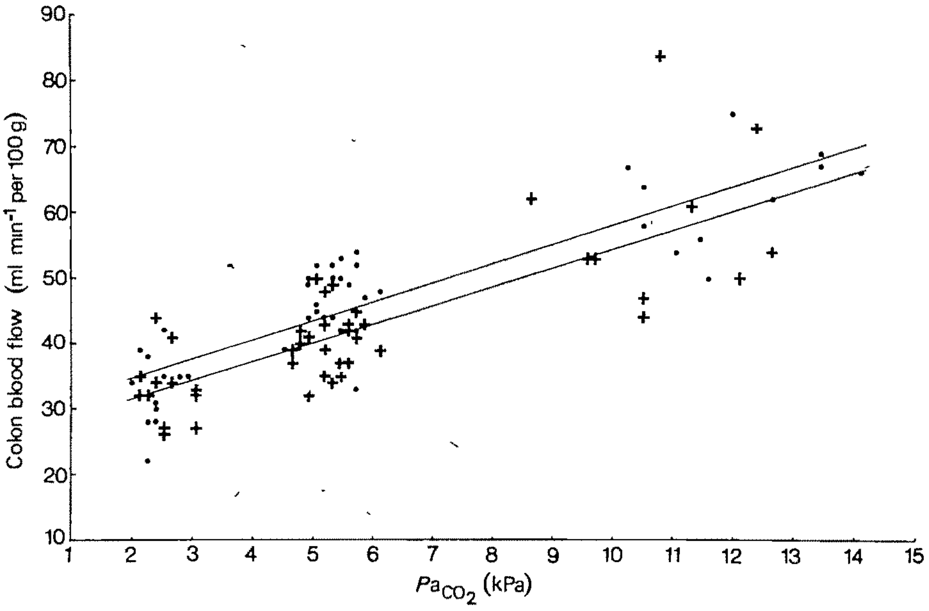

FIG. 1. Colon blood flow plotted against arterial $P\text{CO}_2$, before and after spinal nerve block. + = Before block slope = 2.86, constant = 25.82, $r = 0.776$. ● = Block: slope = 3.13, constant = 28.21, $r = 0.846$. Comparison of slopes: $t = 0.59$, d.f. = 91.

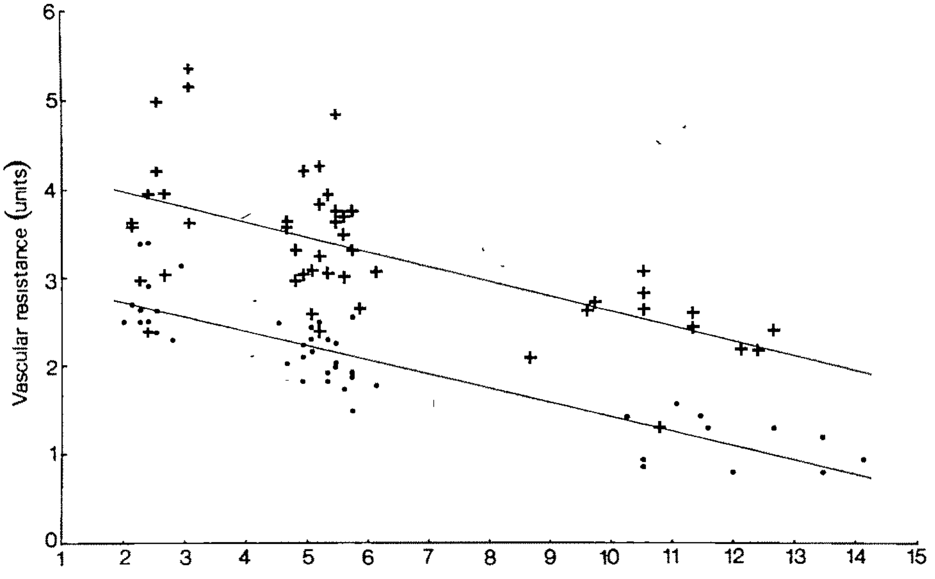

FIG. 2. Colon vascular resistance plotted against arterial $P\text{CO}_2$ before and after spinal nerve block. + = Before block: slope = −0.17, constant = 4.33, $r = -0.628$. ● = Block: slope = −0.16, constant = 3.05, $r = -0.874$. Comparison of slopes: $t = 0.25$, d.f. = 91.

following the block, colon blood flow was significantly increased at all ranges of arterial $P\text{CO}_2$. In figure 2, the relationship between colon vascular resistance and arterial $P\text{CO}_2$ is demonstrated. A good correlation coefficient was obtained again both before and after spinal nerve block.

DISCUSSION

The effects of spinal nerve block

In the present study, subarachnoid spinal nerve block was associated with a 44% decrease in colon vascular resistance. Despite a considerable decrease in mean arterial pressure, this produced a highly significant increase in colon blood flow. The decrease in total peripheral resistance was 31%, which is of a greater order than that found by Sancetta and others (1952) in humans having high spinal nerve block, with a sensory level above T4, although Pugh and Wyndham (1950) found decreases in total peripheral resistance of up to 35% in patients with a similar level of block. It was difficult to determine the exact level of spinal nerve block in the dogs in the present study, but the fact that bradycardia occurred suggests that the sympathetic cardiac fibres were being affected, and therefore that the level of block was probably up to the mid-thoracic region, thus making it equivalent to a "high" spinal anaesthetic. The dogs were also receiving a general anaesthetic agent, which would reduce the reflex vasoconstriction in the upper part of the body, exaggerating the decrease in total peripheral resistance. Nevertheless, the decrease in colon vascular resistance was greater than that in total peripheral resistance. This is contrary to the findings of Mueller, Lynn and Sancetta (1952), who found no significant change in splanchnic vascular resistance during high spinal anaesthesia at a time when total peripheral vascular resistance was decreased.

As the arterial oxygen tension and content remained unchanged before and after spinal nerve block, the 22% increase in colon blood flow resulted in a similar percentage increase in oxygen availability. The colon venous $P\text{O}_2$, which probably reflects accurately the end-capillary $P\text{O}_2$, was significantly increased, and it seems reasonable to suggest that the capillary–tissue $P\text{O}_2$ gradient would be correspondingly increased. The arterial–colon venous oxygen content difference was substantially decreased, but despite the increase in colon blood flow, colon oxygen consumption was decreased by an average of 17%. This may be because of decrease in metabolic activity following the removal by spinal nerve block of central sympathetic and parasympathetic stimulation. (The parasympathetic nerve supply to the dog colon is from the sacral roots.)

Effects of carbon dioxide changes

The effects on colon blood flow and vascular resistance, and the effects on heart rate, mean arterial pressure and total peripheral resistance, of hypocapnia and hypercapnia before subarachnoid spinal nerve block in the present study are comparable to those reported previously (Gilmour et al., 1980) using the same model. That work also demonstrated that changes in colon blood flow in response to hypocapnia occur in response to the alteration in carbon dioxide tension, and are not a result of haemodynamic changes caused by hyperventilation itself. In the present study, hypocapnia produced a slightly greater decrease in arterial pressure and colon blood flow after spinal nerve block, whereas hypercapnia following spinal nerve block resulted in a large decrease in arterial pressure, which was reflected in a smaller percentage increase in colon blood flow than that seen before the block, even though the absolute value was greater. Colon vascular resistance was less after spinal nerve block, irrespective of the value of arterial $P\text{CO}_2$.

A number of points of interest are raised by these findings. First, sympathetic nerve block did not produce maximal vasodilatation in the colon vasculature, since an increase in arterial $P\text{CO}_2$ produced a further decrease in vascular resistance. This confirms earlier findings by Folkow (1949) and Pappenheimer (1952) in other parts of the body. Second if, in the colon, changes in vascular resistance following alterations to arterial $P\text{CO}_2$ are a result of the direct effects of carbon dioxide on the vessels, partly countered by the effects of the sympathetic nervous system acting in the opposite direction, then it would be expected that the sympathetic denervation produced by spinal nerve block would result in larger alterations in vascular resistance in response to changes in $P\text{CO}_2$, since the direct effects of carbon dioxide should be unopposed. However, in the present study, the changes in colon vascular resistance in response to hypocapnia and hypercapnia were similar before and after the block. It is possible that the concentration of circulating catecholamines in the blood will still change in response to alterations in arterial $P\text{CO}_2$, despite the fact that the adrenal medulla is denervated by high spinal nerve block. However, it is unlikely that circulating catecholamine concentrations have a significant effect on colon vessel tone, and it would seem reasonable to assume that sympathetic compensation afforded to the colon vasculature against the effects of carbon dioxide is minimal.

Clinical applications

If the findings of the present study are applicable in man it would appear that high spinal nerve block may provide the colon with an increased blood supply and oxygen availability. Patients who are anaesthetized using a muscle relaxant–nitrous oxide–analgesic technique tend to be artificially hyperventilated, producing small arterial $P\text{CO}_2$ values of 3.5–4 kPa which will reduce colon blood flow and oxygen availability. Most anaesthetists using high spinal nerve block as an anaesthetic technique allow the patient to breathe spontaneously, partly as an aid in detection of the height of the block, but also because abdominal relaxation is so profound that muscle relaxants are unnecessary. Under these conditions, the patient's arterial $P\text{CO}_2$ has been shown to increase slightly to values of up to 7.2 kPa (Morgan and Norman, 1975). It would appear from the present study that this combination will produce a substantially increased colon blood flow. Spinal nerve block by extradural catheter after operation would be expected to combine good analgesia with an improved blood flow to the anastomosis. Because of the relationship between blood flow and anastomotic healing, these techniques may be able to contribute to a reduction in the frequency of anastomotic dehiscence.

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EFFETS DU BLOCAGE DU NERF RACHIDIEN SUBARACHNOIDE ET DU $P\text{CO}_2$ ARTERIEL SUR LA CIRCULATION DU SANG DU COLON CHEZ LE CHIEN

RESUME

On a mesuré les changements intervenus dans la circulation sanguine au niveau du colon répondant à de fortes modifications du $P\text{CO}_2$ artériel, avant et après le blocage du nerf rachidien. Le courant sanguin du colon augmenta de façon significative après le blocage du nerf rachidien, indépendamment du $P\text{CO}_2$. Ces résultats peuvent présenter une importance clinique pour l'homme.

AUSWIRKUNGEN VON SUBARACHNOIDALSPINALNERVBLOCKADE UND ARTERIELLER $P\text{CO}_2$ AUF DEN DICKDARM-BLUTKREISLAUF BEIM HUND

ZUSAMMENFASSUNG

Vor und nach der Spinalnervblockade wurden Änderungen im Dickdarm-Blutkreislauf von Windhunden gemessen, die als Reaktion auf akute Änderungen der arteriellen $P\text{CO}_2$ eintraten. Der Durchfluss im Dickdarm nahm nach der Spinalnervblockade bedeutend zu, unabhangig von der $P\text{CO}_2$. Der Befund konnte eventuell von klinischer Bedeutung fur den Menschen sein

EFECTOS DEL BLOQUEO DEL NERVIO RAQUIDEO SUBARACNOIDEO Y $P\text{CO}_2$ ARTERIAL SOBRE EL FLUJO SANGUINEO DEL COLON EN PERROS

SUMARIO

Se midieron los cambios del flujo sanguíneo del colón de perros galgos en respuesta a agudas modificaciones del $P\text{CO}_2$ arterial antes y después del bloqueo del nervio raquídeo. El flujo sanguíneo del colón aumentó significativamente después del bloqueo del nervio raquídeo, independientemente del $P\text{CO}_2$. Estos resultados pueden tener importancia clínica para el hombre.

Br. J. Anaesth. (1980), 52, 1079

EFFECTS OF ENFLURANE AND HALOTHANE ON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION IN THE GREYHOUND

R. L. HUGHES, D. CAMPBELL AND W. FITCH

SUMMARY

The effects of increasing inspired concentrations of halothane 0.5, 1.0, 1.5, 2.0% and enflurane 1.0, 1.5, 2.0, 3.0% on the hepatic circulation, were investigated in two groups of anaesthetized greyhounds Hepatic arterial and portal venous blood flow were measured continuously using electromagnetic flow probes. Mean arterial pressure and cardiac output were monitored throughout each investigation. At equipotent anaesthetic concentrations there were similar and dose-dependent decreases in hepatic arterial, portal venous and total liver blood flows in both groups. Enflurane produced a more marked decrease in mean arterial pressure than halothane because of a significant decrease in systemic vascular resistance. Hepatic arterial resistance decreased significantly with enflurane but was unchanged in the group receiving halothane. Neither drug affected hepatic oxygen consumption significantly.

Halothane has been in widespread use as a volatile general anaesthetic agent since its introduction in 1956 (Raventos, 1956). However, over the past few years there has been increasing suspicion that it produces hepatic damage, possibly because of a reductive metabolite of the drug (Cousins et al., 1978; Inman and Mushin, 1978; McLain, Sipes and Brown, 1979; Ross, Daggy and Cardell, 1979). Enflurane (Ēthrane) has been available since 1966 (Virtue et al., 1966) but only since 1978 in the U.K. Since no cases of hepatic damage by enflurane have been documented reliably (Black, 1979), it has been suggested that this agent should be substituted for halothane when repeated inhalation anaesthetics are necessary or when any suspicion of compromised liver function exists.

An animal model has been described by the authors to allow the study of the effect of various factors upon liver blood flow and oxygen consumption (Hughes et al., 1979a). We have compared the effects of equipotent anaesthetic concentrations (MAC equivalents) of enflurane and halothane upon this model. MAC has been shown to be 0.87% halothane (Eger et al., 1965) and approximately 2% enflurane (Merin, Kumazawa and Luka, 1976) in dogs. Therefore, the effects of halothane and enflurane upon the variables under study have been compared at approximately equipotent anaesthetic concentrations over the range used in clinical practice.

MATERIALS AND METHODS

Anaesthesia was induced in greyhounds (20–30 kg), after overnight fasting, with thiopentone 20 mg kg^{-1} and maintained subsequently with pentobarbitone 30 mg kg^{-1} i.v. Anaesthesia was maintained by further supplements of pentobarbitone. Pancuronium bromide 0.15 mg kg^{-1} i.v. was administered at the commencement of the procedure to allow muscle relaxation during laparotomy. Following tracheal intubation the lungs were ventilated artificially (Barnet Mark II ventilator) with a mixture of nitrogen 75% in oxygen at a rate of 12 b.p.m. with an inspiratory–expiratory ration of 1 : 2. The minute volume and the inspired oxygen concentrations were adjusted as necessary to maintain normal arterial carbon dioxide and oxygen tensions.

Operative procedure

This has been described in detail previously (Hughes et al., 1979a). Following laparotomy a 3-mm electromagnetic flow probe (Statham) was applied to the hepatic artery, a 6-mm probe to the portal vein and a 3-mm flow probe to the splenic vein.

The electromagnetic flowmeters were calibrated *in vivo* using blood of haematocrit greater than 40 (Hughes et al., 1979b). Electronic zero was checked using balloon occluders from time to time in each experiment. The gastroduodenal artery, the

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0007-0912/80/111079-08 $01.00

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right gastric artery and the gastroduodenal vein were ligated. The stump of the gastroduodenal vein was cannulated to allow blood sampling and measurement of portal venous pressure. The hepatic vein was cannulated via the external jugular vein to allow the measurement of hepatic venous pressure and to permit blood sampling.

Cardiac output was measured with the thermal dilution method using a triple-lumen thermistor-tipped catheter (Devices) placed in the pulmonary artery. Hepatic oxygen consumption was calculated using the oxygen content values of portal venous, hepatic venous and arterial blood measured with the Lex-O_2-Con electrolytic cell (Lexington Instruments):

$$\text{Hepatic oxygen consumption (ml min}^{-1}\text{)} = \left(\frac{\text{Portal venous blood flow}}{100} \times (\text{portal venous} - \text{hepatic venous O}_2\text{content})\right) + \left(\frac{\text{hepatic arterial blood flow}}{100} \times (\text{hepatic arterial} - \text{hepatic venous O}_2\text{ content})\right)$$

where portal venous and hepatic arterial blood flows are in ml min^{-1}.

Total peripheral vascular resistance, hepatic arterial resistance and mesenteric vascular resistance were calculated using the following equations:

$$\text{Total peripheral resistance (TPR)} = \frac{\text{mean arterial pressure (MAP) (mm Hg)}}{\text{cardiac output (litre min}^{-1}\text{)}}$$

$$\text{Hepatic arterial resistance (HAR)} = \frac{\text{MAP} - \text{hepatic venous pressure (mm Hg)}}{\text{hepatic arterial blood flow (ml min}^{-1}\text{)}}$$

$$\text{Mesenteric vascular resistance (MVR)} = \frac{\text{MAP} - \text{portal venous pressure (mm Hg)}}{\text{portal venous blood flow (ml min}^{-1}\text{)}}$$

Arterial blood-gas tensions and the acid–base status of the animals were measured using a Corning 165 blood-gas/pH analyser. The haematocrit was measured at hourly intervals to ensure that it remained greater than 40. The liver was removed at the end of each experiment and weighed.

Experimental programme

(A) *Halothane experiments.* Six greyhounds were prepared as described above.

Approximately 3 h after the induction of anaesthesia, baseline control values were determined at Pa_{O_2} 13.3 kPa and Pa_{CO_2} 5.3 kPa. The base excess was maintained at −4 mmol litre^{-1} as this appears to be the normal value for dogs (Zweens et al., 1977). Halothane was added to the inspired gas mixture from a Fluotec Mk II (Cyprane) temperature-compensated vaporizer at concentrations of 0.5%, 1%, 1.5% and 2%. Each concentration was given for 30 min. Hepatic arterial blood flow, portal venous blood flow and mean aterial pressure were measured continuously and measurements of these and all the other indices under study were taken after 30 min administration of halothane. The concentration of halothane was then increased and measurements repeated after a further 30 min. The preparation was not returned to control between each administration of halothane. Arterial blood was sampled after each 30 min of halothane and analysed for blood halothane concentrations using gas–liquid chromatography by the method of Allott, Steward and Mapleson (1971).

(B) *Enflurane experiments.* In a second group of six greyhounds, enflurane (Ethrane) was administered by means of an Enfluratec (Cyprane) temperature-compensated vaporizer at concentrations of 1%, 1.5%, 2% and 3%. A procedure similar to the halothane experiments was followed, that is enflurane was given at each increasing concentration for 30 min, not returning to control between each concentration. Arterial blood samples were taken at the end of each 30-min period of administration and analysed for blood enflurane concentration by a solvent extraction method similar to that used in the halothane experiments.

The statistical analysis was performed on absolute values relative to the control value using a paired *t* test.

RESULTS

(A) *Halothane experiments.* Mean arterial pressure decreased in a linear fashion from the control of 122 mm Hg with increasing concentrations of halothane (fig. 1). Cardiac output decreased in a similar manner with increasing concentrations of halothane (table I).

Portal venous blood flow decreased significantly with each concentration of halothane from the control value of 137 ml per 100 g liver to a

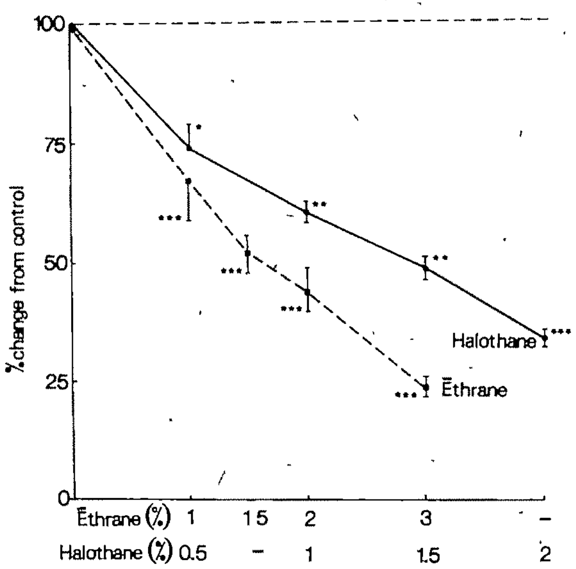


FIG. 1. Effect of equipotent concentrations of halothane and enflurane (Ēthrane) on mean arterial pressure. The values are shown as percentages of the control. Bars indicate ±SEM $^*P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$ relative to control. $n=6$ in each group.

minimum value of 45% of control with 2% halothane (fig. 2A).

There was a greater percentage decrease in hepatic arterial flow from control of 38 ml per 100 g liver to a value 35% of control with 2% halothane (fig. 2B). Total liver blood flow decreased in a manner similar to portal venous blood flow (fig. 2C).

There were small decreases in peripheral resistance which were not significant (fig. 3). Hepatic arterial resistance did not change significantly with any concentration of halothane (fig. 4). There were no significant changes in mesenteric vascular resistance (table I).

There was a small decrease in hepatic oxygen consumption with each concentration of halothane which did not reach significance. There was no significant change in hepatic or portal venous pressure (table I). Splenic venous blood flow decreased rapidly until it could not be measured with the e.m. flow probe.

The arterial halothane concentrations achieved after each 30-min administration are stated in table II.

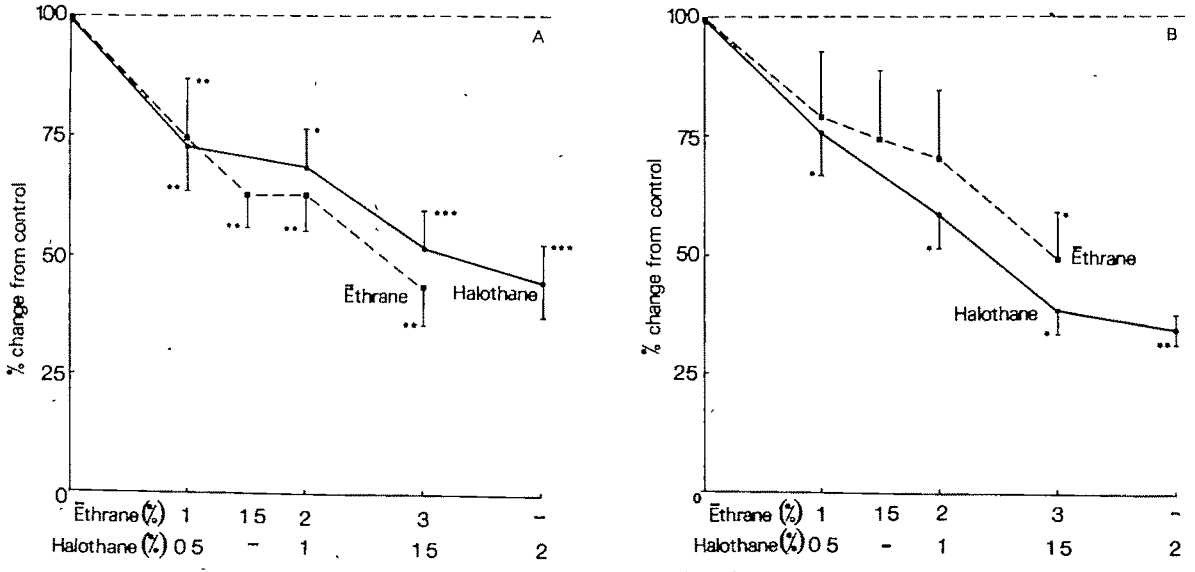
(B) *Enflurane experiments.* Mean arterial pressure decreased from control of 122 mm Hg to 24% of control with 3% enflurane (fig. 1). Cardiac output decreased linearly with increasing concentrations of enflurane (table III).

Portal venous blood flow decreased significantly with each concentration of enflurane from the control value of 112 ml per 100 g liver to a minimum value of 44% of control with 3% enflurane (fig. 2A). Hepatic arterial blood flow decreased significantly only at the 3% enflurane concentration from a control of 27.1 ml per 100 g liver weight (fig. 2B). Total liver blood flow decreased in a manner similar to portal venous blood flow (fig. 2C). As with halothane, splenic venous blood flow decreased to values which could not be detected soon after the introduction of enflurane.

Peripheral resistance decreased significantly with each concentration of enflurane (fig. 3).

TABLE I. *Effect of four concentrations of halothane on cardiac output, hepatic oxygen consumption, mesenteric vascular resistance, hepatic venous pressure and portal venous pressure. Values are ±SEM. Significant differences from control:* $^{**}P<0.01$; n = 6

		Halothane concentration (%)			
	Control	0.5	1	1.5	2
Cardiac output	0.155	0.125	0.122	0.084**	0.066**
(litre min^{-1} kg^{-1})	±0.019	±0.008	±0.008	±0.006	±0.003
Hepatic oxygen consumption	5.0	4.18	4.57	4.19	4.42
(ml min^{-1} per 100 g)	±0.87	±0.48	±0.74	±0.65	±0.42
Mesenteric vascular resistance	0.151	0.158	0.139	0.150	0.116
(mm Hg^{-1} ml^{-1} min)	±0.011	±0.014	±0.019	±0.026	±0.017
Hepatic venous pressure	3.05	2.91	3.36	3.05	3.7
(mm Hg)	±1.01	±1.13	±0.74	±1.08	±0.74
Portal venous pressure	7.73	7.25	7.38	6.5	6.86
(mm Hg)	±1.23	±1.23	±1.34	±1.38	±1.48



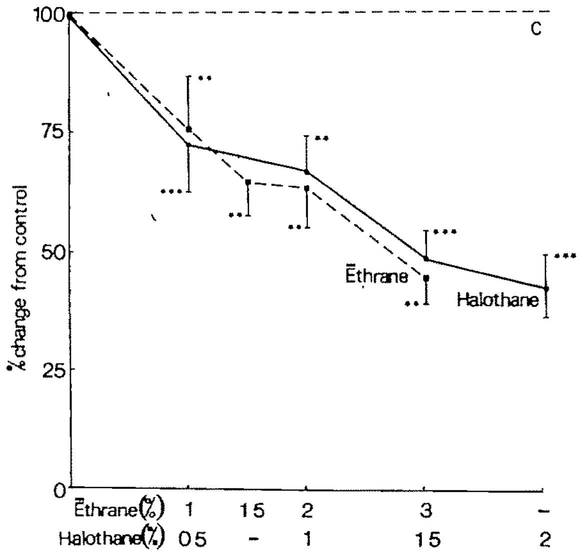


FIG. 2. Effect of equipotent concentrations of halothane and enflurane (Ethrane) on (A) portal venous blood flow (B) hepatic arterial blood flow and (C) total liver blood flow. The values are shown as percentages of the control. Bars indicate ±SEM. $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$ relative to control. $n=6$ in each group.

Hepatic arterial resistance decreased significantly with 1.5 and 3% enflurane (fig. 4). Mesenteric vascular resistance decreased significantly with 2% and 3% enflurane (table III).

There were no significant changes in hepatic oxygen consumption with any concentration of enflurane. There were no significant changes in portal or hepatic venous pressure (table III). The arterial enflurane concentrations after 30-min administration are given in table II.

Comparison of effects of halothane and enflurane

The effects of halothane and enflurane have been plotted together for comparison. Statistical analyses were made using absolute values and an unpaired Student's *t* test. Minimum alveolar concentrations (MAC) have been plotted to allow comparison of equipotent anaesthetic doses.

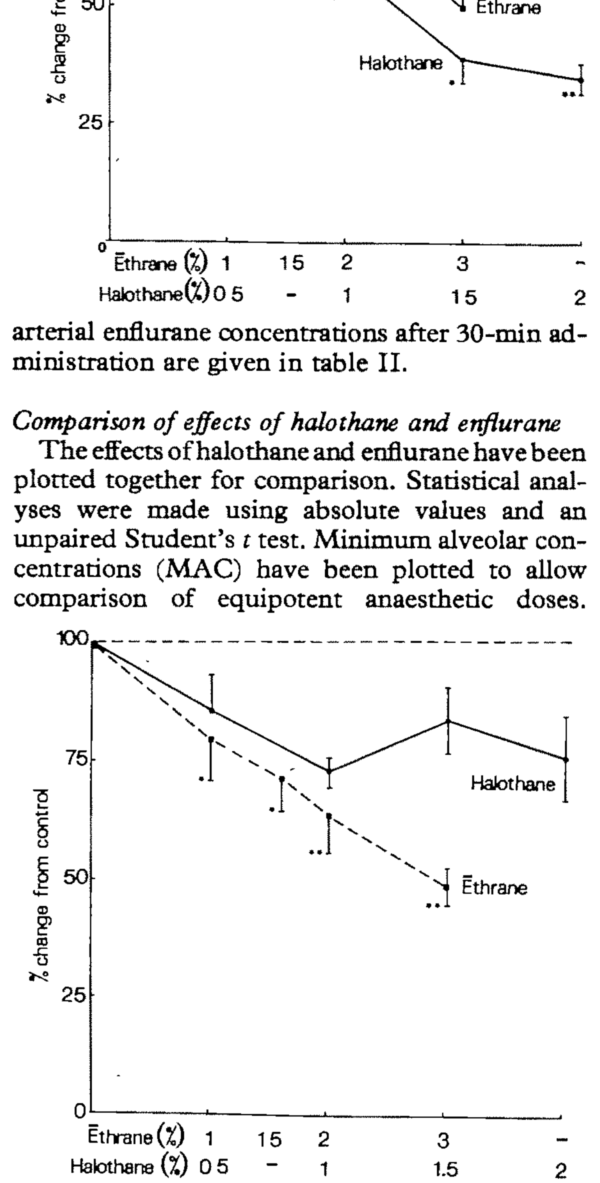


FIG. 3. Effect of equipotent concentrations of halothane and enflurane (Ethrane) on total peripheral resistance. The values are shown as percentages of the control. Bars indicate ±SEM. $^{*}P<0.05$; $^{**}P<0.01$ relative to control. $n=6$ in each group

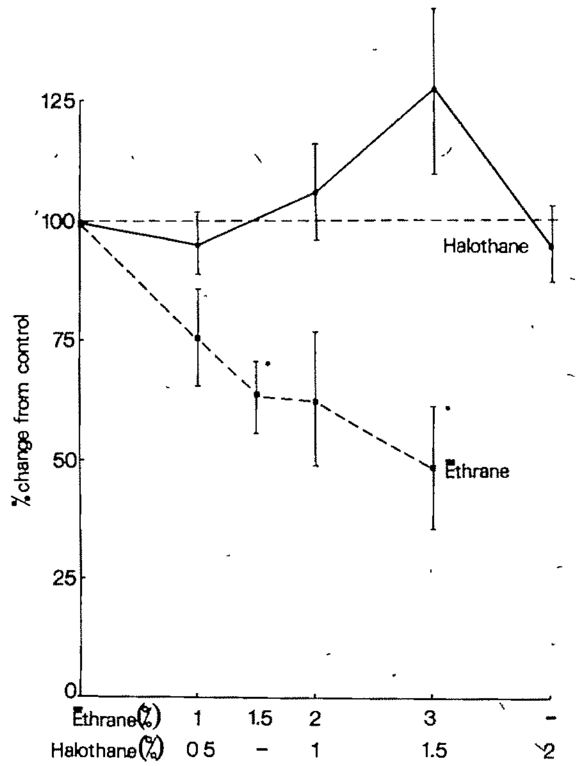


FIG. 4. Effect of equipotent concentrations of halothane and enflurane (Ethrane) on hepatic arterial resistance. The values are shown as percentages of control. Bars indicate ±SEM. $^*P<0.05$. $n=6$ in each group.

There were no significant differences between the control enflurane and halothane values (tables I, III and IV). However, there was a large, although not statistically significant, difference between the control hepatic arterial blood flow values and therefore hepatic arterial resistance.

There were significant differences ($t = 3.85$) between the mean arterial pressure achieved with 2% enflurane and 1% halothane and 3% enflurane and 1.5% halothane ($t = 8.06$) (fig. 1).

There were no significant differences in portal venous, hepatic arterial and total liver blood flow at equipotent concentrations. There was a significant difference in peripheral resistance between halothane 1.5% and enflurane 3% ($t=5.15$) (fig. 3).

There were large differences which were not statistically significant between the effects of enflurane and halothane upon hepatic arterial resistance (fig. 4).

DISCUSSION

The administration of increasing concentrations of halothane produced significant and dose-dependent decreases in haemodynamic variables in both the systemic (mean arterial pressure, cardiac output) and hepatic (hepatic arterial blood flow, portal venous blood flow, total liver blood flow) circulations. Hepatic arterial resistance did not change significantly. Decreases in hepatic arterial blood flow, portal venous blood flow and total liver blood flow were observed as a result of the administration of increasing concentrations of enflurane. In addition, enflurane produced dose-dependent decreases in mean arterial pressure and cardiac output. Unlike halothane, enflurane induced significant decreases in hepatic arterial and systemic vascular resistances.

Halothane

Previous investigations have demonstrated that the administration of halothane produced progressive decreases in total liver blood flow, in association with parallel decreases in cardiac output (Ahlgren et al., 1967; Deutsch, 1967; Juhl and Einer-Jensen, 1974). Decreases of 50–60% in hepatic arterial blood flow and portal venous blood flow have been observed at mean arterial halothane concentrations of 20–40 mg dl^{-1} (produced by 30 min administration of halothane 1.5% (approx.))

TABLE II. *Arterial concentrations (± SD) of halothane after each 30-min administration of 0.5%, 1%, 1.5% and 2%, and arterial concentrations (± SD) of enflurane after each 30-min administration of 1%, 1.5%, 2% and 3%* (n = 6 *for each agent*)

	Control	Concentration administered (%)				
		0.5	1	1.5	2	3
Arterial halothane concn (mg dl^{-1})	0	10.72 ±2.72	17.52 ±2.24	23.98 ±2.65	29.23 ±4.7	— —
Arterial enflurane concn (mg dl^{-1})	0	— —	15.97 ±0.99	21.47 ±0.99	29.42 ±1.8	40.59 ±0.71

TABLE III. *Effect of four concentrations of enflurane on cardiac output, hepatic oxygen consumption, mesenteric vascular resistance, hepatic venous pressure and portal venous pressure Significant differences from control·* *P<0.05, **P<0.01; ***P<0.001. *Values are* ±*SEM.* n=6

		Enflurane concentration (%)			
	Control	1	1.5	2	3
Cardiac output (litre min^{-1} kg^{-1})	0.139 ±0.009	0.114** ±0.008	0.102** ±0.005	0.093** ±0.005	0.071*** ±0.005
Hepatic oxygen consumption (ml min^{-1} per 100 g)	3.67 ±0.52	3.74 ±0.59	3.64 ±0.25	3.79 ±0.53	3.13 ±0.36
Mesenteric vascular resistance (mm Hg ml^{-1} min)	0.196 ±0.026	0.178 ±0.032	0.160 ±0.025	0.128* ±0.016	0.099** ±0.014
Hepatic venous pressure (mm Hg)	1.78 ±0.73	1.8 ±0.56	2.25 ±0.68	2.5 ±0.49	3.42 ±0.57
Portal venous pressure (mm Hg)	4.75 ±0.85	4.55 ±0.63	3.85 ±0.56	3.95 ±0.64	4.08 ±0.59

TABLE IV. *Control values of mean arterial pressure, portal venous blood flow, hepatic arterial blood flow, peripheral resistance and body weight obtained in the enflurane and halothane groups. Values are* ±*SEM.* n=6 *in each group*

	Enflurane	Halothane
Mean arterial pressure (mm Hg)	122.2±8.8	121.8±8.8
Portal venous blood flow (ml per 100 g)	112.0±15.8	136.7±14.2
Hepatic arterial blood flow (ml per 100 g)	27.1±6.2	38.6±5.5
Peripheral resistance (mm Hg litre^{-1} min)	36.5±4.12	38.5±4.9
Weight (kg)	24.3±2.1	25.8±1.5

(Thulin, Andreen and Irestedt, 1975; Andreen, Irestedt and Zetterstrom, 1977).

Reciprocity in response has been shown in a variety of conditions, between portal venous and hepatic arterial blood flows (Hanson and Johnson, 1966; Hanson, 1973) such that there is a concomitant decrease in hepatic arterial resistance as portal venous blood flow is decreased. Thus the oxygen supply to the liver is protected. In the present study, halothane produced a decrease in portal venous blood flow and a slight increase in hepatic arterial resistance. A similar, small increase in resistance was observed initially by Thulin, Andreen and Irestedt (1975) although they demonstrated a much greater increase in resistance in a subsequent study (Andreen, Irestedt and Zetterstrom, 1977). The small, but not significant, decrease in hepatic oxygen consumption supports the results reported previously by Theye, Kuster and Dawson (1972) and Andreen, Irestedt and Thulin (1975).

Enflurane

The effects of enflurane on hepatic arterial blood flow, portal venous blood flow and hepatic oxygen consumption, were similar to those described by Irestedt and Andreen (1979) following the administration of enflurane 2.2%. However, in contrast to halothane, hepatic arterial resistance was noted to decrease significantly with enflurane.

Comparison between halothane and enflurane

A randomly allocated cross-over study would have been the most appropiate design to allow a precise comparison between the effects of the two drugs on liver haemodynamics. However, this was not possible because of the marked effects on the systemic circulation produced by the greatest concentrations of the two drugs. For example, it proved impossible to study enflurane 4% (2 MAC) as cardiovascular collapse was produced rapidly in this animal model. Nevertheless, the administrations of halothane and enflurane were interspersed and the anaesthetic technique and surgical preparation were similar in both groups of animals. As the baseline values were similar in the two groups also (table IV) we feel that a tentative comparison of the effects of the two anaesthetic drugs is justified. Since it has been suggested that the minimum alveolar concentration of a volatile anaesthetic agent required to prevent gross movement in response to a painful stimulus might serve as a means of comparing the potency of such drugs (Eger, Saidman and Brandstater, 1965) the variables under study were compared at concentrations of enflurane twice those of halothane (with the exception of enflurane 4%).

An appreciation of the similarities between the effects of halothane and enflurane can be obtained from an examination of figures 2A–C and 3. The principal difference between the drugs was their divergent effects on the hepatic artery (fig. 4). This could be the result of a local effect by which halothane affected adversely the ability of the hepatic arterioles to vasodilate as portal venous blood flow was decreased. However, in view of the different effects of the two drugs on systemic vascular resistance (fig. 3) and mesenteric vascular resistance (tables I, III), it seems likely that this is a generalized, and not a local, phenomenon. Millar and Biscoe (1966) showed that halothane produced an increase in post-ganglionic sympathetic nervous activity in the rabbit and this could be the mechanism which preserves vascular tone in the dog.

Myocardial depression would appear to be the primary cause of the hypotensive effect of halothane, whereas enflurane produced a more marked depression of the cardiovascular system by effects on both the myocardium and vascular smooth muscle. In any consideration of the influence of the two drugs on the systemic circulation it must be noted that the results were obtained in the artificially ventilated and normocapnic dog. If the animals had been studied while breathing spontaneously the resultant hypercapnia could have produced an increase in cardiac output (Price, 1960; Calverley et al., 1978a) which would have counteracted the effects of the anaesthetic agents themselves.

A comparison of halothane and enflurane in spontaneously breathing patients failed to demonstrate any difference between their effects on the cardiovascular system (Ascorve et al., 1976). However, studies of enflurane in man (Calverley et al., 1978b) and in the dog (Merin, Kumazawa and Luka, 1976; Horan et al., 1977) during controlled (normocapnic) ventilation, showed that greater cardiovascular depression was produced by enflurane than by halothane. In addition, Prys-Roberts and colleagues (1974) demonstrated in man that halothane had an insignificant effect on systemic vascular resistance.

ACKNOWLEDGEMENTS

This investigation was supported by a grant from the Scottish Hospitals Endowment Research Trust. Technical assistance was provided by Mr D McMillan and Mr F Toal. The assistance of Miss Diane E. McCorkindale in typing the manuscript is noted with appreciation.

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EFFETS DE L'ENFLURANE ET DE L'HALOTHANE SUR LA CIRCULATION SANGUINE DU FOIE ET LA CONSOMMATION D'OXYGENE CHEZ DES LEVRIERS

RESUME

Des recheches ont été effectuées chez deux groupes de lévriers anesthésiés en ce qui concerne les effets de concentrations inspirées croissantes d'halothane à 0,5%, 1,0%, 1,5% et 2,0% et d'enflurane à 1,0%, 1,5%, 2,0% et 3,0%. Au moyen de sondes électromagnétiques de circulation, on a mesuré continuellement la circulation de l'artère hépatique et de la veine porte. Au cours de chaque expérience, un contrôle de la fonction cardiaque et de la pression artérielle moyenne a été assuré. Pour des concentrations anesthétiques de puissance égale, on a observé dans les deux groups des baisses analogues en rapport avec le dosage en ce qui concerne la circulation artérielle hépatique, celle de la veine porte et la circulation hépatique totale. L'enflurane a provoqué une baisse plus marquée de la pression artérielle moyenne que ne l'avait fait l'halothane, ceci en raison d'une réduction significative de la résistance vasculaire systémique. La résistance artérielle hépatique a baissé de manière significative sous l'effet de l'enflurane alors qu'elle demeurait inchangée dans le groupe auquel on avait administré de l'halothane Aucune de ces deux substances n'a eu d'effet marqué sur la consommation d'oxygène.

EINWIRKUNG VON ENFLURAN UND HALOTHANE AUF DEN LEBERBLUTKREISLAUF UND LEBERSAUERSTOFFVERBRAUCH BEI WINDHUNDEN

ZUSAMMENFASSUNG

Die Auswirkungen einer Zunahme eingeatmeter Konzentrationen von Halothan 0,5, 1,0, 1,5 und 2,0% und Enfluran 1,0, 1,5, 2,0 und 3,0% auf den Leberblutkreislauf wurden bei zwei Gruppen von narkotisierten Windhunden untersucht. Leberarterien- und Pfortaderdurchfluss wurden standig mittels elektromagnetischer Durchflussmessfuhler gemessen. Der durchschnittliche Arteriendruck und Herzminutenvolumen wurden bei jeder Untersuchung standig uberwacht. Bei gleich starken Narkosekonzentrationen traten bei beiden Gruppen ahnliche dosisabhangige Reduktionen des Leberarterien-, Pfortader- und Gesamtleberdurchflusses auf. Bei Enfluran war die Reduktion des durchschnittlichen Arteriendrucks stärker ausgeprägt als bei Halothan, auf Grund der bedeutenden Reduktion des Gefässwiderstands des Gesamtsystems. Der Leberarterienwiderstand ging bei Enfluran bedeutend zurück, blieb aber unverandert bei den Gruppen, die Halothan bekamen. Weder das eine noch das andere Narkosemittel hatte einen bedeutenden Einfluss auf den Sauerstoffverbrauch der Leber.

EFECTOS DEL ENFLURANO Y DEL HALOTANO EN EL FLUJO SANGUINEO DEL HIGADO Y EN EL CONSUMO DE OXIGENO EN PERROS GALGOS

SUMARIO

En dos grupos de perros galgos bajo anestesia, se averiguó los efectos sobre la circulación hepática de crecientes concentraciones inspiradas de halotano al 0,5%, 1,0%, 1,5% y 2%, y de enflurano al 1,0%, 1,5%, 2,0% y 3,0%. Mediante sondas electro-magnéticas de flujo, se midió constantemente los flujos sanguíneos de la arteria hepática y de la vena porta. A todo lo largo de cada investigación, se controló la presión arterial y el ritmo cárdiaco promedios. Con concentraciones anestéticas de igual potencia, se observaban disminuciones análogas en relación con la dosis tanto de los flujos de la arteria hepática y de la vena porta como del de la sangre hepática total en ambos grupos. El enflurano produjo una reducción de la presión arterial media más marcada que la causada por el halotano, a raíz de una disminución significativa de la resistencia vascular sistémica. La resistencia arterial hepática bajó de manera significante con el enflurano, pero no se modificó en el grupo que recibió halotano Ninguna de estas substancias afectó significativamente al consumo de oxigeno hepático.

Br. J. Anaesth. (1980), 52, 1087

EFFECTS OF ENFLURANE ON CARDIOVASCULAR FUNCTION IN DOGS WITH INDUCED CHRONIC MITRAL VALVE DISEASE

E. Cockings, K. Prasad, B. Bharadwaj and C. L. O'Neil

SUMMARY

The effect of enflurane on cardiovascular function was investigated in normal dogs and in dogs with chronic heart failure because of induced mitral valve disease (MVD). No significant changes were observed in heart rate (HR), right atrial pressure (RAP) and total systemic vascular resistance (TSVR) in normal dogs. However, significant decreases in HR and increases in RAP and TSVR were observed in dogs with MVD. There were no changes in pulmonary arterial pressure and left ventricular end-diastolic pressure in either group. Cardiac output, cardiac index, arterial pressure, left ventricular work index and left ventricular d*p*/d*t* and d*p*/d*t*IIP showed a concentration-dependent decrease in both groups but the changes were greater in dogs with MVD.

Enflurane has been reported to produce a dose-dependent decrease in cardiovascular function in healthy man (Beer et al., 1973; Tarnow et al., 1974; Calverley et al., 1978a; Calverley et al., 1978b; Smith et al., 1978), monkey (Ritzman, Erickson and Miller, 1976) and dog (Merin, Kumazawa and Luka, 1976; Horan et al., 1977). A dose-dependent decrease in myocardial contractility has also been observed in *in vitro* studies with cat papillary muscle from a healthy heart (Shimosato et al., 1969; Iwatsuki, Shimosato and Etsten, 1970; Brown and Crout, 1971). A negative inotropic effect of this agent on cat papillary muscle from failing hearts has been reported by Kemmotsu, Hashimoto and Shimosato (1974). However, studies in man have indicated that enflurane has a minimal negative inotropic effect (Levesque et al., 1974) or no effect (Marshall et al., 1971) on the myocardium.

Our unpublished observation indicates that the failing heart is very sensitive to the effect of pentobarbitone and the negative inotropic effect of an inhalation anaesthetic may be increased. However, no significant differences in the enflurane-induced decrease in contractility of papillary muscle from normal and failing hearts were reported by Kemmotsu, Hashimoto and Shimosato (1974). Although enflurane is used frequently during open heart surgery, no data are available on the effects of enflurane on cardiovascular function in the failing heart with chronic mitral valve disease (MVD).

The cardiovascular effects of various doses of enflurane in dogs with healthy hearts and in dogs with induced MVD were investigated to determine if cardiovascular changes are similar in these two conditions.

METHODS

Experiments were carried out on five normal dogs (18–24.4 kg) of either sex and six dogs (18–26.6 kg) with induced chronic MVD. MVD was induced by the method of Prasad, Khatter and Bharadwaj (1977). Two or more chorda tendinae were detached from the anterior cusps of the valve through the left atrial route to increase the left atrial pressure to 2.5 to 3 times the control value. These dogs exhibited a typical pansystolic murmur and forceful left ventricular thrust, left ventricular and left atrial enlargement, and mild to moderate interstitial pulmonary oedema on chest x-ray (fig. 1A, B). The cardiovascular effects of enflurane were investigated in this second group 8–9 months after surgery.

All the dogs had been fasting for 12 h before the experiment and received no premedication. A Teflon catheter was introduced to a foreleg vein. Diazepam 2.0 mg kg^{-1} was administered i.v. for sedation. Diazepam in this dose produces minimal

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0007-0912/80/111087-10 $01.00

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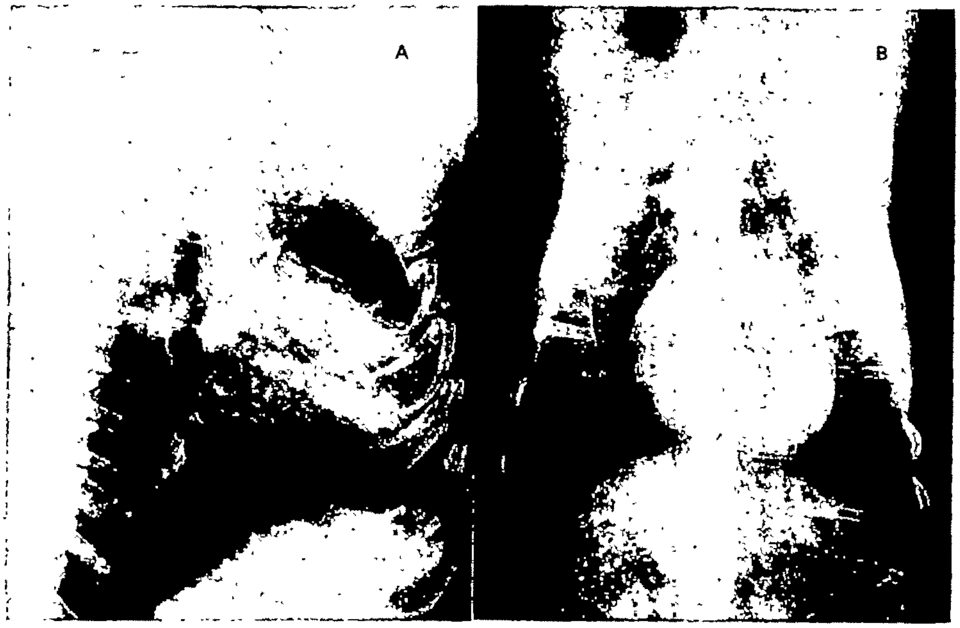

FIG. 1. Dog with induced mitral insufficiency. A: Lateral thoracic radiograph. The heart is increased in the apico-basilar dimension, resulting in dorsal elevation of the trachea. The left cardiac border is straightened and is accompanied by loss of the caudal waist. The pulmonary vasculature appears congested. B: Dorsoventral thoracic radiograph. The heart is abnormally rounded with prominent bulging of the left ventricular border. The overlying scapulae falsely create the impression of a cranial middle lobe infiltrate

haemodynamic effects (Starley and Michie, 1969). A light plane of anaesthesia was then produced with 70% nitrous oxide in oxygen administered by mask using a Bain circuit (Bain and Spoerel, 1972) with a total fresh gas flow of 175 ml kg^{-1} (Soliman and Laberge, 1978).

Lignocaine 1 mg kg^{-1} in a 1% solution was infiltrated s.c. over the femoral pulse, and the femoral artery and vein were exposed for haemodynamic and blood-gas studies. Ventricular, aortic (AP), right atrial (RAP), pulmonary arterial (PAP) and pulmonary arterial wedge (PAWP) pressures were recorded with Ailtech microdot pressure transducers and a Beckman R411 dynograph recorder. A 7 French gauge Cournand (Cordis GF) catheter was positioned at the aortic arch via the femoral artery to record AP. The same catheter was pushed into the left ventricle to record the left ventricular (LV) pressure. A balloon-tipped pulmonary artery catheter (7 French gauge) was positioned in the right atrium through the femoral vein to record RAP and to inject cardiogreen dye for cardiac output (CO) determination. The same catheter was used to record right ventricular (RV) and pulmonary artery pressure (PAP). The recording apparatus was calibrated to give a 1-mm deflection for 4 mm Hg for pressures in the LV and aorta; and 1-mm deflection for 1 mm Hg for other pressures. These pressures were recorded at a frequency response of 100 Hz. The first derivative of left or right ventricular pressure dp/dt was recorded with a differentiating device coupled to ventricular pressures at a frequency response of 100 Hz.

Integrated isovolumetric pressure (IIP) is the area (mm Hg s), under the rising limb of the isovolumeteric phase of intraventricular pressure development corresponding to 1.5 times the duration from the peak of the R wave of the lead II e.c.g. to the maximum point of the dp/dt curve. The ratio dp/dt IIP is a better index of myocardial contractility than dp/dt because it is not affected by preload or by a small change in the heart rate (Siegel et al., 1964; Yang et al., 1972). The ratio of dp/dt is affected by contractility, preload, afterload and heart rate (Siegel et al., 1964; Yang et al., 1972). The ratio dp/dtIIP was used, therefore, as one of the measures of myocardial contractility

(Siegel et al., 1964; Yang et al., 1972; Prasad, Khatter and Bharadwaj, 1979). The first derivative of ventricular pressures, dp/dt, standard limb lead II e.c.g. and ventricular pressure curves were recorded simultaneously for determination of this index.

CO was determined in duplicate by the indicator dilution technique. Cardiogreen was injected into the right atrium and the arterial blood sampled from the cannula positioned in the aortic arch at a constant rate. The indicator dilution curve was obtained using a Waters cuvette densitometer. The haemodynamic data were obtained by the methods described by Prasad, Khatten and Bharadwaj (1977) and Koob and Prasad (1978). Left ventricular work index (LVWI) was obtained from the following formula:

$$\text{LVWI (kg.m min}^{-1}\text{ m}^2) = \text{MSAP} \times \text{CI} \times 0.0136$$

where MSAP = mean systolic arterial pressure (mm Hg), CI = cardiac index, and 0.0136 = conversion factor.

Total systemic vascular resistance (TSVR) was calculated using the following formula:

$$\text{TSVR (dyne s cm}^{-5}) = \frac{(\text{mAP} - \text{mRAP}) \times 80}{\text{CO}}$$

Where mAP = mean aortic pressure (mmHg), CO = cardiac output (litre min^{-1}), mRAP = mean right atrial pressure and 80 = conversion factor.

Blood-gas analysis (pH and $P\text{CO}_2$) was performed with an IL (Instrument Laboratory) 113-SI analyser. Control haemodynamic variables were recorded after the nitrous oxide was discontinued and the dogs were breathing only 100% oxygen and were quiet and awake. Control blood samples were also taken for blood-gas analysis.

The dogs were then anaesthetized with enflurane 1.76% and the trachea was intubated with a cuffed tube. A Monaghan model 300 ventilator was used to maintain a respiratory rate of 12 b.p.m. and a tidal volume of 10 ml kg^{-1}. These variables were monitored by an electronic Wright spirometer. Pa_{CO_2} was maintained close to normal values by adjusting the fresh gas inflow through the Bain circuit (Bain and Spoerel, 1977) and monitoring the end-tidal carbon dioxide with a Godart infra-red analyser.

Muscle paralysis was achieved by a continuous infusion of suxamethonium 1 mg $\text{kg}^{-1}\text{h}^{-1}$, a dose which has little effect on the cardiovascular function (Merin, Kumazawa and Luka, 1976). Body temperature was recorded continuously using an oesophageal thermistor probe.

Five inspired concentrations of enflurane (1.15, 1.76, 2.26, 2.98 and 3.48%) were used in both the normal and MVD dogs. For each dose study, the inspired concentration was first set at 0.25% greater than the concentration at which the cardiovascular variables were to be measured for 15 min. The enflurane concentration was then reduced to the concentration under study and maintained for 30 min, when various cardiovascular variables were measured and samples taken for blood-gas analysis. The enflurane vaporizer was calibrated by means of a Miran analyser and the calibration rechecked at the end of the study.

The results were analysed using a paired t test; unpaired t test was used for comparisons between the normal and the stenotic animals. Two types of comparison were made: before and after enflurane administration in the same group of dogs and between normal dogs and dogs with MVD after enflurane administration.

RESULTS

Aortic, pulmonary artery, pulmonary arterial wedge, and right atrial pressures

The effects of various concentrations of enflurane on AP, PAP, PAWP and RAP in normal dogs and in dogs with chronic MVD are shown in tables I and II.

All the concentrations of enflurane produced a significant decrease in diastolic AP in normal dogs. Significant decreases in mean AP were observed only when the concentration of enflurane was 1.76% and greater. Systolic AP decreased but was significant only at 1.15, 2.98 and 3.48% of enflurane. There were no significant changes in mean PAP and mean PAWP at any concentration of enflurane Mean RAP decreased significantly only at 1.15, 1.76 and 2.26% of enflurane.

In dogs with chronic MVD, enflurane 1.15% did not produce any significant change in the AP. Concentrations of enflurane of 1.76% and greater produced significant decreases in systolic, diastolic and mean AP. None of the concentrations of enflurane produced any significant change in the mean PAP or PAWP. RAP increased significantly with enflurane concentrations of 2.26%

The changes in AP, mean PAP and mean PAWP in dogs with MVD were not significantly different

TABLE I. *Effects of enflurane on cardiovascular function in normal dogs. The values represent mean ± SEM.* *$P<0.05$, **$P<0.01$; †$P<0.02$; ***$P<0\,001$, ‡$P<0.002$

Measurement	Control	Inspired enflurane (%)				
		1.15	1.76	2.26	2.98	3.48
Aortic systolic pressure (mm Hg)	138 ± 9	120 ± 10†	126 ± 11	116 ± 14	88 ± 6**	85 ± 4***
Aortic diastolic pressure (mm Hg)	98 ± 7	80 ± 8†	78 ± 8*	73 ± 6**	61 ± 8**	50 ± 4***
Mean pulmonary arterial pressure (mm Hg)	13 ± 1	12 ± 2	12 ± 0	15 ± 2	14 ± 1	12 ± 2
Total systemic vascular resistance (dyne s cm^{-5})	2689 ± 156	2701 ± 120	2658 ± 171	2742 ± 89	2792 ± 143	2601 ± 120
Left ventricular systolic pressure (mm Hg)	157 ± 12	146 ± 7	137 ± 6†	123 ± 6†	104 ± 7**	90 ± 6**
Left ventricular end-diastolic pressure (mm Hg)	12 ± 0	11 ± 1	9 ± 2	10 ± 1	11 ± 1	14 ±2
Right ventricular systolic pressure (mm Hg)	26 ± 2	27 ± 2	24 ± 3	25 ± 3	22 ± 3**	22 ± 3
Right ventricular end-diastolic pressure (mm Hg)	5 ± 1	6 ± 1	4 ± 0	6 ± 1	6 ± 1	10 ± 1
Mean right atrial pressure (mm Hg)	6 ± 0	3 ± 1**	3 ± 0***	4 ± 1*	6 ± 1	7 ± 1
Heart rate (beat min^{-1})	116 ± 5	112 ± 6	115 ± 7	115 ± 7	118 ± 8	118 ± 6

TABLE II. *Effects of enflurane on cardiovascular function in dogs with chronic mitral valve disease. The values represent mean ±SEM.* *$P<0.05$; **$P<0\,01$; †$P<0.02$; ***$P<0.001$; ‡$P<0.002$

Measurement	Control	Inspired enflurane (%)				
		1.15	1 76	2.26	2.98	3.48
Aortic systolic pressure (mm Hg)	148 ± 5	144 ± 7	132 ± 8*	122 ± 9**	101 ± 7***	95 ± 7*
Aortic diastolic pressure (mm Hg)	105 ± 4	104 ± 7	94 ± 7	90 ± 6†	74 ± 6**	61 ± 6*
Mean pulmonary arterial pressure (mm Hg)	21 ±3	21 ± 2	19 ± 2	19 ± 3	21 ± 1	23 ± 3
Total systemic vascular resistance (dyne s cm^{-5})	2677 ± 211	3190 ± 174*	3285 ± 151	4214*	4326*	4343*
Left ventricular systolic pressure (mm Hg)	173 ± 7	168 ± 3	155 ± 10	133 ± 8***	105 ± 5***	84 ± 7‡
Left ventricular end-diastolic pressure (mm Hg)	19 ± 3	19 ± 2	17 ± 2	17 ± 2	18 ± 2	20 ± 2
Right ventricular systolic pressure (mm Hg)	38 ±3	38 ± 2	36 ± 2	32 ± 3	31 ± 3	28 ± 3
Right ventricular end-diastolic pressure (mm Hg)	6 ±1	7 ± 1	6 ± 1	6 ± 1*	7 ± 0*	11 ± 2
Mean right atrial pressure (mm Hg)	4 ± 1	5 ± 1	5 ± 1	7 ± 0	7 ± 0	8 ± 1*
Heart rate (beat min^{-1})	148 ± 4	130 ±7**	128 ± 6**	122 ± 5**	118 ± 5**	110 ± 8*

than from those in normal dogs. However, the increases in RAP were significantly greater in the dogs with MVD than those in normal dogs at all concentrations of enflurane.

Total systemic resistance and heart rate

None of the concentrations of enflurane produced any significant change in TSVR in normal dogs (table I). However, enflurane in all concentrations produced a significant increase in TSVR in dogs with MVD (table II). These increases were significantly greater in dogs with MVD than in normal dogs.

There was no significant change in HR with any concentration of enflurane in normal dogs (table I). HR in dogs with MVD was significantly greater than in normal dogs. Enflurane in all concentrations produced significant and concentration-dependent decreases in HR (table II).

Cardiac index and left ventricular work index

The effects of enflurane on CI and LVWI are summarized in figure 2. Enflurane produced a concentration-dependent decrease in CI but the decreases in normal dogs were significant only at a concentration of 2.26% and greater. However, in dogs with chronic MVD, enflurane produced a concentration-dependent decrease in CI and the decreases were significant at all concentrations. The decreases in CI in dogs with MVD were significantly greater than in normal dogs at concentrations of 1.76% and more.

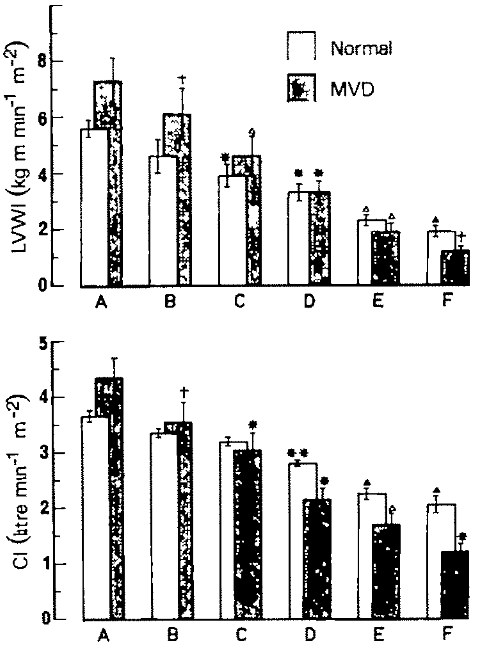

FIG. 2. Effects of enflurane on the cardiac index (CI) and left ventricular work index (LVWI) in normal dogs and in dogs with mitral valve disease (MVD). A = control, before enflurane. B, C, D, E, and F after 1.15, 1.76, 2.26, 2.98, and 3.48% and of enflurane respectively $^*P<0.05$; $^\dagger P<0.01$, $\Delta P<0.02$.

There were concentration-dependent decreases in the LVWI in both normal dogs and dogs with MVD (fig. 2). While the decreases were significant only in concentrations of 1.76% and more in normal dogs, the decreases were significant with all concentrations in the dogs with MVD. The decreases in LVWI were significantly greater in dogs with MVD than in normal dogs with concentrations of 2.98% and greater.

Ventricular pressures

The effects of enflurane on left ventricular (LV) and right ventricular (RV) end-diastolic and systolic pressures in normal dogs and in dogs with MVD are summarized in tables I and II.

There was a tendency for a concentration-dependent decrease in LV systolic pressures in both normal dogs and dogs with MVD. However, the decreases were significant at concentrations of 1.76% and more in normal dogs, and at 2.26% and more in dogs with MVD. The decreases in systolic pressure were significantly greater in dogs with MVD than in normal dogs at concentrations of 2.26% and more. There was no significant change in LV end-diastolic pressure either in normal dogs or in dogs with MVD.

There were no significant changes in the RV systolic pressure in either normal dogs or dogs with MVD at any concentration except at 2.98% and 3.48% of enflurane in normal dogs and at 3.48% of enflurane in dogs with MVD, where the decreases were significant. The decreases were not significantly different in the two groups. No significant changes in RV end-diastolic pressure were observed in either group.

Left ventricular d*p*/d*t and* d*p*/d*t*IIP

The effects of various concentrations of enflurane on LV d*p*/d*t* and d*p*/d*t*IIP are given in figure 3. Although there was a tendency for a concentration-dependent decrease in d*p*/d*t* in normal dogs, the decreases were significant only at concentration of 2.26% and greater of enflurane. LV d*p*/d*t* was significantly less in dogs with MVD than in normal dogs before enflurane anaesthesia. Enflurane produced a concentration-dependent significant decrease in LV d*p*/d*t*. The decreases in d*p*/d*t* were significantly greater in dogs with MVD

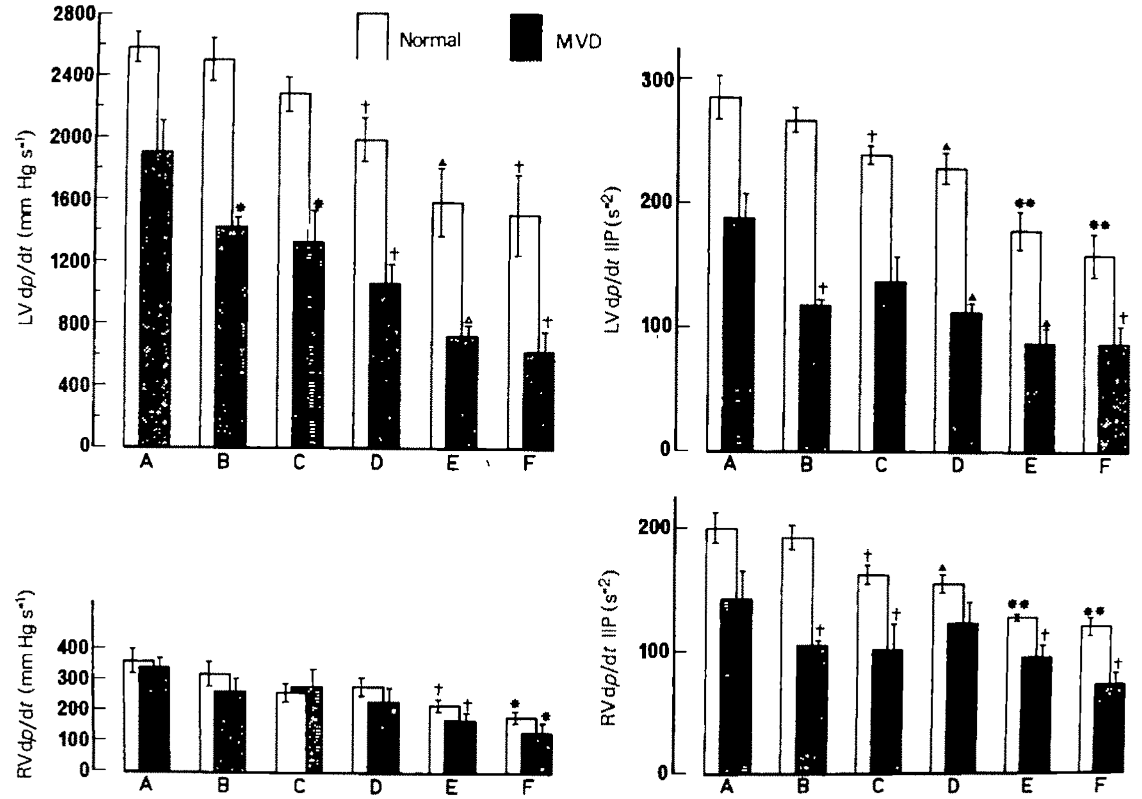

FIG. 3. Effects of enflurane on the left ventricular (LV) and right ventricular (RV) $\mathrm{d}p/\mathrm{d}t$ and $\mathrm{d}p/\mathrm{d}t$ IIP in normal dogs and in dogs with mitral value disease (MVD). The other notations are the same as in figure 2.

than those in normal dogs at all concentrations.

There was a dose-dependent decrease in LV $\mathrm{d}p/\mathrm{d}t$ IIP in normal dogs, but the decreases were significant only at concentrations of 1.76% and greater. LV $\mathrm{d}p/\mathrm{d}t$ IIP was significantly less in dogs with MVD than that in normal dogs before enflurane anaesthesia. Enflurane produced a significant concentration-dependent decrease in LV $\mathrm{d}p/\mathrm{d}t$ IIP at all concentrations except 1.76%. The decreases in LV $\mathrm{d}p/\mathrm{d}t$ IIP in dogs with MVD were more than those in normal dogs at all concentrations except at 1.76% enflurane.

Right ventricular $\mathrm{d}p/\mathrm{d}t$ *and* $\mathrm{d}p/\mathrm{d}t$ *IIP*

The effects of enflurane on RV $\mathrm{d}p/\mathrm{d}t$ and $\mathrm{d}p/\mathrm{d}t$ IIP in normal dogs and in dogs with MVD are summarized in figure 3. Enflurane produced significant decreases in $\mathrm{d}p/\mathrm{d}t$ in both groups of dogs at concentrations of 2.98% and more. The decreases were not significantly different from each other. Enflurane produced significant decreases in $\mathrm{d}p/\mathrm{d}t$ IIP at concentrations of 1.76% and more in normal dogs. The decreases in $\mathrm{d}p/\mathrm{d}t$ IIP in dogs with MVD were significant at all concentrations except 2.26% of enflurane.

Haematocrit, temperature and blood-sugar

The changes in the haematocrit, temperature and blood-sugar concentration during enflurane anaesthesia in normal dogs and in dogs with MVD are summarized in tables III and IV.

The haematocrit decreased progressively with greater concentrations in both normal dogs and dogs with MVD. This might possibly be caused by haemodilution as a result of fluid administration during cardiac catheterization and continuous i.v. infusion. The temperature remained constant during the experiments. There was concentration-dependent decrease in the blood-sugar in both

TABLE III. *Effects of enflurane on normal dogs*

	Inspired enflurane (%)					
Measurements	Control	1.15	1.76	2.26	2.98	3.48
Arterial haematocrit (%)	38.6 ± 1.40	38.8 ± 2.13	35.4 ± 1.60	34.2 ± 1.53	33.8 ± 1.20	32.8 ± 1.07
Temperature (°C)	37.6 ± 0.19	37.6 ± 0.17	37.7 ± 0.21	37.6 ± 0.16	37.6 ± 0.18	37.4 ± 0.19
Arterial blood sugar (mg%)	122.4 ± 1.91	97.0 ± 5.29	94.4 ± 3.70	81.4 ± 7.59	76.8 ± 7.77	76.6 ± 5.44
Arterial P_{CO_2} (kPa)	4.87 ± 0.28	4.83 ± 0.35	4.94 ± 0.34	5.11 ± 0.21	4.97 ± 0.34	4.89 ± 0.14
Arterial pH (units)	7.39 ± 0.01	7.36 ± 0.02	7.36 ± 0.01	7.35 ± 0.01	7.34 ± 0.01	7.32 ± 0.01

TABLE IV. *Effects of enflurane on dogs with mitral valve disease*

	Inspired enflurane (%)					
Measurement	Control	1.15	1.76	2.26	2.98	3.48
Arterial haemotocrit (%)	39.7 ± 1.73	39.7 ± 1.78	38.3 ± 1.56	37.3 ± 1.41	35.2 ± 1.28	35.5 ± 0.84
Temperature (°C)	37.5 ± 0.18	37.5 ± 0.16	37.5 ± 0.28	37.5 ± 0.17	37.3 ± 0.25	37.4 ± 0.17
Arterial blood sugar (mg%)	123.3 ± 9.7	99.7 ± 5.1	92.0 ± 5.5	86.3 ± 7.4	77.5 ± 5.9	77.5 ± 6.5
Arterial P_{CO_2} (kPa)	4.72 ± 0.13	4.72 ± 0.15	4.76 ± 0.20	4.62 ± 0.14	4.63 ± 0.22	4.62 ± 0.09
Arterial pH (units)	7.36 ± 0.01	7.33 ± 0.02	7.36 ± 0.01	7.32 ± 0.01	7.34 ± 0.01	7.30 ± 0.07

normal and MVD dogs. These changes were similar in both groups.

Arterial P_{CO_2} *and pH*

There were no significant changes in arterial P_{CO_2} during enflurane anaesthesia in either group of dogs (tables III, IV). However, blood pH decreased in both groups especially during the greatest concentration of enflurane. Blood pH before enflurane anaesthesia was less in the dogs with MVD than in normal dogs.

DISCUSSION

This study deals with the effect of five concentrations of enflurane on cardiovascular function in normal dogs and in dogs with MVD. In previous studies (Merin, Kumazawa and Luka, 1976) in normal dogs, only two concentrations (2.3 and 3.6%) were used. Studies of the effects of enflurane on some cardiovascular functions have been performed on awake dogs (Merin, Kumazawa and Luka, 1976) and Rhesus monkey (Ritzman, Erickson and Miller, 1976) with implanted catheters. To assess the effects of anaesthetics on cardiovascular function, measurement of control valves should be made in the awake animal. In this study control measurements were made while dogs were breathing 100% oxygen and were quiet and sedated.

The LV systolic pressures were always greater than the AP. This was not because of any undetected aortic stenosis, but could be explained by:

(i) the catheter may have obstructed the flow of blood through the aortic valve and slightly increased LV systolic pressure; (ii) it may have been an artefact caused by resonance. However, we feel that the first explanation is more plausible.

The control HR in normal dogs were less than those in dogs with MVD. This is expected since there is a compensatory increase in HR in cardiac failure caused by MVD (Prasad, Khatter and Bharadwaj, 1977). The control HR in normal dogs was also lower than reported by Merin, Kumazawa and Luka (1976). Enflurane did not produce any significant change in HR in normal dogs. It did, however, produce a concentration-dependent decrease in HR in dogs with MVD. Studies of the effects of enflurane on HR in normal animals are conflicting and difficult to explain. Merin, Kumazawa and Luka (1976) observed an increase in HR in dogs at both concentrations (2.3 and 3.6%). Ritzman, Erikson and Miller (1976), however, observed a concentration-dependent decrease in HR in the monkey.

Some of the indices of cardiac pump performance (CO, CI and LVWI) decreased while others (LV and RV end-diastolic pressure) did not change with enflurane in both normal and MVD dogs. The decreases in CO and CI with enflurane were consistent with the findings of Merin, Kumazawa and Luka (1976) in dogs, Ritzman, Erickson and Miller (1976) in the monkey, and Karliczek and others (1974) in man. The decreases in pump performance were greater in dogs with MVD than in normal dogs, indicating that the failing heart was more sensitive to the depressant effect of enflurane. CO and CI are affected not only by mycocardial contractility but also by preload, afterload and heart rate (Siegel et al., 1964; Yang et al., 1972). Hence cardiac performance does not necessarily indicate the condition of the myocardium.

Control RV end-diastolic pressures were similar in both groups of dogs. However, control LV end-diastolic pressures in dogs with MVD were greater than in the normal dogs, suggesting that the left ventricle was in failure because of MVD (Prasad, Khatter and Bharadwaj, 1977). It is surprising that LV and RV end-diastolic pressures did not change with enflurane. In dogs with MVD the change may not be seen because of the increased compliance of the ventricle (Mason et al., 1972). Merin, Kumazawa and Luka (1976) observed a decrease with small concentrations and an increase with large concentrations of enflurane, of the mean left atrial pressure. In general the index of cardiac muscle performance (LV and RV d*p*/d*t*, d*p*/d*t*IIP) decreased with enflurane in both groups of dogs. The results are consistent with the findings of Merin, Kumazawa and Luka (1976) in normal dogs, Ritzman, Erickson and Miller (1976) in normal monkey and Karliczek and others (1974) in healthy man. It is known that d*p*/d*t* is affected by preload, afterload, heart rate and contractility (Yang et al., 1972). Hence d*p*/d*t* is not a reliable index of myocardial contractility. The ratio d*p*/d*t* IIP is a better index of myocardial contactility than d*p*/d*t*, because it excludes the preload factor and is not affected by a small change in HR (Siegel et al., 1964; Yang et al., 1972). Both d*p*/d*t* and d*p*/d*t* IIP decreased more in dogs with MVD than in normal dogs, indicating that the myocardium of dogs with MVD is more vulnerable to the effect of enflurane.

TSVR in both groups of dogs was similar before enflurane anaesthesia. This is surprising because, in previous studies by Prasad, Khatter and Bharadwaj (1977) TSVR increased in dogs with MVD. This discrepancy might be the result of a marked decrease in CO in previous studies, while in this study CO was greater in MVD dogs than in normal dogs. This might be related to the ventricular hypertrophy and dilation phase before ventricular failure. It was observed that, while enflurane in all concentrations affected the systemic vascular resistance in dogs with MVD, it did not affect this variable in normal dogs.

There was a significant decrease in the haematocrit in both groups of dogs. This may have been caused by flushing during cardiac catheterization and after withdrawal of blood samples, or by continuous slow i.v. infusion. The arterial $P\text{CO}_2$, and body temperature were constant throughout the experiment. The blood pH decreased especially during the greater concentrations of enflurane. This might be caused by lower arterial pressure reducing tissue oxygenation with subsequent increase in lactic acid production. Merin, Kumazawa and Luka (1976) observed an increase in arterial lactate with enflurane anaesthesia.

Blood-glucose concentration decreased consistently with all concentrations of enflurane in both groups of dogs. Merin, Kumazawa and Luka (1976), however, observed a decrease in arterial blood-glucose with small dose and return to normal with a large dose of enflurane.

It appears that enflurane has a concentration-dependent depressant effect on the cardiac pump function and cardiac muscle performance. It is also apparent that the depressant effect of enflurane on the cardiac pump and muscle performance is greater in dogs with MVD than in normal dogs.

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EFFETS DE L'ENFLURANE SUR LA FONCTION CARDIOVASCULAIRE CHEZ DES CHIENS SOUFFRANT DE MALADIE CHRONIQUE INDUITE DE LA VALVULE MITRALE

RESUME

Des recherches ont été effectuées en ce qui concerne les effets de l'enflurane sur la fonction cardiovasculaire chez des chiens normaux et chez des chiens souffrant de décompensation cardiaque chronique dûe à une maladie induite de la valvule mitrale (MVD). Aucune modification significative du rythme cardiaque (HR), de la pression atriale droite (RAP) et de la résistance vasculaire systémique totale (TSVR) ne fut observée chez les chiens normaux. Toutfois, on observa des diminutions de HR et des augmentations de RAP et de TSVR significatives chez les chiens souffrant de MVD. Aucun changement ne se produisit en ce qui concerne la pression artérielle pulmonaire et la pression diastolique-terminale ventriculaire gauche dans les deux groupes. La fonction cardiaque, l'indice cardiaque, la pression artérielle, l'indice de fonctionnement ventriculaire gauche ainsi que le d*p*/d*t* ventriculaire gauche et d*p*/d*t*IIP (IIP = pression isovolumétrique intégrée) enregistrèrent une baisse en rapport avec le concentration dans les deux groupes, mais les modifications furent plus importantes chez les chiens souffrant de MVD.

EINWIRKUNG VON ENFLURAN AUF DIE KARDIOVASKULÄRE FUNKTION BEI HUNDEN MIT INDUZIERTER CHRONISCHER HERZKLAPPENAFFEKTION

ZUSAMMENFASSUNG

Die Einwirkung von Enfluran auf die kardiovaskulare Funktion normalen Hunden und Hunden mit chronischer, durch induzierte Mitralklappenaffektion hervorgerufener Herzmuskelschwäche wurde untersucht. Es wurden keine bedeutende Änderungen der Herzschlage pro Minute, des rechten Vorhofdrucks und des Gefässwiderstands des Gesamtsystems bei normalen Hunden festgestellt. Es wurden jedoch bedeutende Reduktionen der Herzschläge pro Minute und Steigerungen des rechten Vorhofdrucks und des Gefässwiderstands des Gesamtsystems bei Hunden mit Mitralklappenaffektion festgestellt. Bei keiner der beiden Gruppen traten Anderungen des Lungenarteriendrucks und des linken ventrikulären enddiastolischen Drucks ein. Herzminutenvolumen, Herzindex, Arteriendruck, linke ventrikulare Arbeitspulssumme und linke ventrikulare dp/dt und dp/dt-integrierten isovolumetrischen Druck wiesen eine konzentrationsabhangige Reduktion bei beiden Gruppen auf, jedoch waren diese Änderungen bei Hunden mit Mitralklappenaffektion stärker ausgepragt.

EFECTOS DEL ENFLURANO EN LA FUNCTION CARDIOVASCULAR DE PERROS PADECIENDO DE ENFERMEDAD CRONICA INDUCIDA DE LA VALVULA MITRAL

SUMARIO

Se averiguó en perros normales asi como en perros padeciendo de trastornos cárdiacos crónicos resultantes de la enfermedad inducida de la válvula mitral (MVD), el efecto del enflurano sobre la función cardiovascular. No se observó ningún cambio significante del ritmo cárdiaco (HR), de la presión atrial derecha (RAP), ni tampoco de la resistencia vascular sistémica total (TSVR) en perros normales. Sin embargo, se anotaron disminuciones significantes en el HR y aumentos del RAP y del TSVR en los perros con MVD No se produjo ningún cambio de la presión arterial pulmonar ni de la presión diastólica-terminal ventricular izquierda en cualquiera de los grupos. En ambos grupos, se observó una disminución relacionada con la concentración tanto del rendimiento cárdiaco, del indice cárdiaco, de la presión arterial, del índice de functionamiento ventricular izquierdo como del dp/dt ventricular izquierdo y del dp/dtIIP (IIP = presión isovolumétrica integrada), aunque las modifaciones fueron mayores en los perros con MVD.

Br. J. Anaesth. (1980), 52, 1097

DO NEOSTIGMINE AND 4-AMINOPYRIDINE INHIBIT THE ANTIBACTERIAL ACTIVITY OF ANTIBIOTICS?

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SUMMARY

Neostigmine and 4-aminopyridine are used to antagonize the neuromuscular blockade induced by antibiotics or an antibiotic–non-depolarizing blocker combination. They may also counteract the antibacterial activity of antibiotics. It was found that neostigmine and 4-aminopyridine do not interfere with antibacterial activity of antibiotics in bacterial cultures using an agar solution method. It is concluded that neostigmine and 4-aminopyridine may be used to antagonize neuromuscular blockade induced by antibiotics alone or in combination with non-depolarizing agents.

The neuromuscular blocking effects of antibiotics and their interaction with neuromuscular blocking agents are well known (Timmerman, Long and Pittinger, 1959; Pittinger and Adamson, 1972; Singh, Harvey and Marshall, 1978). The resulting blockade is reversible in some cases by cholinesterase inhibitors or calcium (Van Nijhuis, Miller and Fogdall, 1976; Booij, Miller and Crul, 1978; Singh, Harvey and Marshall, 1978), depending on the antibiotic administered. It has been demonstrated that in most circumstances 4-aminopyridine can reverse the neuromuscular blockade induced by antibiotic–myoneural blocker combination (Booij, Miller and Crul, 1978; Burkett et al., 1979). Antibiotics are administered more frequently in the operative period than previously and it is important to know whether reversing a blockade, induced or prolonged by antibiotics, with cholinesterase inhibitors and 4-aminopyridine, influences the antibacterial effects of antibiotics. In this study we determined the effect of neostigmine and 4-aminopyridine on antibiotic-treated bacterial cultures.

METHOD

The minimal inhibitory concentration (MIC) of antibiotics with and without addition of 4-aminopyridine or neostigmine or both, was determined with an agar dilution method. The antibiotics studied were netilmycin, gentamicin, tobramycin, sisomycin, neomycin, lincomycin and clindamycin.

The antibiotics, 4-aminopyridine 100 ng ml^{-1} and neostigmine 3 μg ml^{-1} were mixed in the agar. Fresh Mueller-Hinton agar supplemented with 5% sheep blood or Schaedler agar, or both, were used for culture of aerobic and facultative anaerobic species. Drug solutions were added in a ratio of one part of drug solution to nine parts of medium; a control plate without drugs was included. The bacterial suspensions used were 6-h cultures of the individual strains tested in tryptone soya broth diluted to a MacFarland 0.5 turbidity standard. The agar plates were inoculated using a Denley A 400 Multipoint Inoculator with approximately 1.3×10^5 colony forming units on each spot. Each agar plate was inoculated with three reference strains (ATCC or NCTC) and with freshly isolated strains from patients. After 17 h incubation at 37 °C the MIC was obtained (Barry, 1976).

RESULTS

The bacterial strains on which the MIC was determined are summarized in table I.

Addition of 4-aminopyridine or neostigmine, or both, in concentrations of 100 ng ml^{-1} and 3 μg ml^{-1} respectively, which are suggested to be peak plasma concentrations (Cronnelly et al., 1979; S. Agoston, personal communication) did not alter MIC significantly (tables II, III).

DISCUSSION

Addition of neostigmine and 4-aminopyridine to Schaedler and Mueller-Hinton agar to produce concentrations equal to the peak plasma concentration after i.v. administration (Cronnelly et al., 1979; S. Agoston, personal communication) did not influence the antibacterial activity of antibiotics tested. The administration of neostigmine

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0007-0912/80/111097-04 $01.00

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TABLE I. *Bacterial cultures and antibiotics tested.* + = *tested,* − = *not tested*

Culture		Netil	Genta	Tobra	Siso	Neo	Linco	Clinda
1 *Pseudomonas aeruginosa*	ATCC 27853	+	+	+	+	+	−	−
2 *Escherichia coli*	ATCC 25922	+	+	+	+	+	−	−
3 *Staphylococcus aureus*	ATCC 25923	+	−	−	−	+	+	+
4 *Streptococcus pneumoniae*	clin. isol. 2x	+	+	+	+	+	−	−
5 *S. Aureus*	clin. isol. 3x	+	−	+	+	+	−	−
6 *E. coli*	clin. isol. 2x	+	+	+	+	+	−	−
7 *Klebsiella* spp.	clin. isol. 3x	+	+	+	+	+	−	−
8 *P. aeruginosa*	clin. isol. 3x	+	+	+	+	+	−	−
9 *Enterobacter* spp.	clin. isol. 2x	+	+	+	+	+	−	−
10 *Proteus mirabilis*	clin. isol.	+	+	+	+	+	−	−
11 Indol-positive *Proteus* spp.	clin. isol	+	+	+	+	+	−	−
12 *Bacteroides fragilis*	NCTC 9343	−	−	−	−	−	+	+
13 *Bacillus subtilis*	ATCC 6633	−	−	−	−	−	+	+
14 *Listeria monocytogenes*	clin. isol.	−	−	−	−	−	+	+
15 *Clostridium perfringens*	clin isol. 4x	−	−	−	−	−	+	+
16 *B. fragilis* subsp. *fragilis*	clin. isol. 2x	−	−	−	−	−	+	+
17 *B. fragilis* subsp. *thetaiotaomicron*	clin. isol.	−	−	−	−	−	+	+
18 *Bacteroides vulgatus*	clin. isol. 2x	−	−	−	−	−	+	+
19 *Bacteroides melaninogenicus asaccharolyticus*	clin. isol.	−	−	−	−	−	+	+
20 *Bacteroides distasonis*	clin. isol.	−	−	−	−	−	+	+
21 *Peptostreptococcus anaerobius*	clin. isol	−	−	−	−	−	+	+
22 *Fusobacterium mortiferum*	clin. isol.	−	−	−	−	−	+	+
23 *Strep. viridans*	clin isol	−	−	−	−	−	+	+
24 *Strep. faecalis*	clin isol.	−	−	−	−	−	+	+

TABLE II. *MIC (mg litre^{-1}) for the aminoglycosides without and with the addition of 4-aminopyridine 100 ng ml^{-1} (A), neostigmine 3 μg ml^{-1} (B), and both (C). For cultures see table I. Only values which change are given. One step of dilution (half or double the original MIC) is within the range of the method*

Culture No.	Netil				Genta				Tobra				Siso				Neo			
	MIC	A	B	C	MIC	A	B	C	MIC	A	B	C	MIC	A	B	C	MIC	A	B	C
1	2				1				1	0.5	0.5	0.5	0.5				32			
2	0.5				0.5				1				0.5				2			
3	0.25																0.25			
4	2				4				4				2	4	2	2	>8			
4	2				2				8				4				8			
5	0.25								0.25				0.25				0.5	0.25	0.25	0.25
6	1	1	0.5	0.5	0.5	0.5	0.5	0.25	1				0.5				2			
6	0.5				0.5				1	1	0.5	0.5	0.5				2			
7	0.5				0.5				1	0.5	0.5	0.5	0.5	0.5	0.5	0.25	2			
7	0.5				0.5				1	0.5	0.5	0.5	0.5				1			
7	0.5				0.5				2				0.5	0.5	0.5	0.25	>256			
8	16				4				2				4	4	4	2	16	32	32	16
8	4				2				1				1				32			
8	16				4				2				4	4	4	2	16	32	32	16
9	0.25				0.25				0.5				0.5				2	1	1	1
9	0.5				0.5				0.5				0.5	0.5	0.5	0.25	2	1	1	1
10	1				0.5	0.5	0.5	0.25	1				0.5	0.5	0.5	0.25	4			
11	0.5				0.25	0.25	0.5	0.5	0.5				0.5	0.5	0.5	0.25	4			

TABLE III. *MIC (mg litre^{-1}) for lincomycin and clindamycin without and with 4-aminopyridine 100 ng ml^{-1} (A), neostigmine 3 μg ml^{-1} (B) or both (C). For cultures see table I. Only values which are changed are given. One step of dilution (half or double the original MIC) is within the range of the method*

	Lincomycin				Clindamycin			
Culture no.	MIC	A	B	C	MIC	A	B	C
3	2				0.25	0.25	0.125	0.125
12	8				0.125			
13	32				2	2	1	1
14	4				0.25	0.25	0.125	0.25
15	1				0.06	0.06	0.06	0.125
15	8				2			
15	256				256			
15	1				0.125			
16	4				0.125			
16	4				0.06			
17	16	8	16	8	1			
18	2				0.06			
19	0.25				0.25			
20	8				0.5			
21	0.25				0.06	0.06	0.06	0.03
22	0.125				0.03			
23	0.5				0.06			
24	32				32			

and 4-aminopyridine may be beneficial where neuromuscular blockade is caused by antibiotics or their interactions with non-depolarizing neuromuscular blockers. Neostigmine and probably pyridostigmine enhance the blockade produced by aminoglycosides and should therefore be avoided (L. H. D. J. Booij and J. M. J. Rutten, unpblished data). Under these circumstances 4-aminopyridine should be administered. No central nervous system effects occur with doses of 4-aminopyridine up to 0.35 mg kg^{-1}. Higher doses, however, cause agitation and disorientation of the patient (Miller et al., 1979) and should not be used.

It is concluded that neostigmine and 4-aminopyridine can be used to antagonize antibiotic-induced neuromuscular blockage without interfering with antibacterial activity.

ACKNOWLEDGEMENT

The authors thank Mrs Joke v.d. Ros for technical assistance.

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LA NEOSTIGMINE ET L'AMINOPYRIDINE-4 INHIBENT-ELLES L'ACTIVITE ANTI-BACTERIENNE DES ANTIBIOTIQUES?

RESUME

On utilise la néostigmine et l'aminopyridine-4 pour antagoniser le blocage neuromusculaire provoqué par les antibiotiques ou par un mélange bloquant antibiotique non dépolarisant. Elles peuvent également réagir contre l'activité antibactérienne des antibiotiques. On s'est aperçu que la néostigmine et l'aminopyridine-4 ne troublent pas l'activité antibactérienne des antibiotiques dans des cultures bactériennes pour lesquelles on a utilisé la méthode de la solution d'agar-agar. On en conclut qu'il est possible d'utiliser la néostigmine et

l'aminopyridine-4 pour antagoniser le blocage neuromusculaire causé par les antibiotiques seuls ou en mélange avec des agents non dépolarisants.

BAKTERIZIDE WIRKUNG VON ANTIBIOTIKA DURCH NEOSTIGMINE UND 4-AMINOPYRIDINE GEHEMMT?

ZUSAMMENFASSUNG

Neostigmine und 4-Aminopyridine werden zur Bekampfung der neuromuskulären Blockade verwendet, die durch Antibiotika oder eine Kombination von diesen mit nicht-depolarisierenden Blockierungsmitteln hervorgerufen wird. Es ist auch moglich, dass sie der bakteriziden Tätigkeit von Antibiotika entgegenwirken. Es wurde festgestellt, dass Neostigmine und 4-Aminpyridine keinen störenden Einfluss auf die bakterizide Tätigkeit von Antibiotika in Bakterienkulturen ausüben, wenn eine Agarlösungsmethode verwendet wird. Es wird geschlossen, dass Neostigmine und 4-Aminopyridine zur Bekampfung einer neuromuskularen Blockade verwendt werden konnen, die durch Antibiotika—entweder allein oder in einer Kombination mit nicht-depolarisierenden Mitteln—hervorgerufen wurde.

INHIBEN LA ACTIVIDAD ANTIBACTERIAL DE LOS ANTIBIOTICOS LA NEO-ESTIGMINA Y LA AMINOPIRIDINA-4?

SUMARIO

Se usan la neo-estigmina y la aminopiridina-4 para antagonizar el bloqueo neuromuscular inducido por los antibióticos o por una mezcla bloqueadora antibiótica no-depolarizante. Pueden también reaccionar en contra de la actividad antibacterial de los antibióticos Se comprobó que la neo-estigmina y la aminopiridina-4 no interfieren con la actividad antibacterial de los antibióticos en cultivos bacteriales cuando se usó el método de la solución de agar-agar. Se llega a la conclusión de que se pueden utilizar la neo-estigmina y la aminopiridina-4 para antagonizar el bloqueo neuromuscular inducido por los antibióticos solos o en combinación con agentes no-depolarizantes.

Br. J. Anaesth. (1980), 52, 1101

RESPIRATORY EFFECTS OF A NEW OPIATE ANALGESIC, R 39209, IN THE RABBIT: COMPARISON WITH FENTANYL

J. H. Brown, B. J. Pleuvry and B. Kay

SUMMARY

The respiratory effects of R 39209, a new short-acting analgesic, were studied and compared with those of fentanyl, in the rabbit. Minute volume, respiratory frequency and pH, $P\text{CO}_2$ and standard bicarbonate of arterialized venous blood were measured. R 39209 had an earlier peak effect and shorter duration of action than fentanyl, but otherwise the respiratory effects of the two drugs were similar. Fentanyl was between 2 and 3.5 times more potent than R 39209. Repeated doses of R 39209 produced reproducible peak effects even when only 10 min was allowed between administrations.

R 39209, a new, potent, short-acting analgesic agent is currently undergoing both clinical and pharmacological investigation (De Castro et al., 1979). Its chemical structure is similar to that of fentanyl (fig. 1).

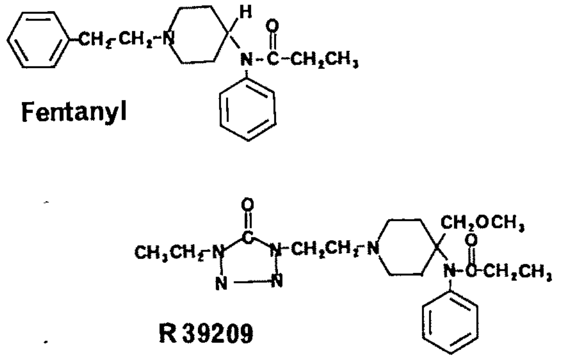

FIG. 1. Chemical structure of R 39209 and fentanyl.

Early reports (Niemegeers, 1977) indicated that R 39209 was approximately four times less potent than fentanyl and a comparative clinical investigation (De Castro, 1977) showed that, in man, R 39209 has a more rapid onset of action and an earlier peak effect than fentanyl, but its duration of action was three times shorter. The safety index for equipotent doses is similar to that of fentanyl.

All reported administrations of R 39209 in man have been accompanied by neuromuscular blockade (suxamethonium for short and pancuronium for longer procedures) and within this concept of "analgesic anaesthesia" (De Castro, 1977), it seemed that R 39209 had no obvious advantages over fentanyl except for short procedures (5–10 min) when the duration of respiratory depression in the period after operation was shorter.

This study compared R 39209 with fentanyl, in respect to effects on respiration in the spontaneously breathing conscious rabbit. In addition selected doses of the two drugs were given repeatedly, over short time intervals, and the reproducibility of the response determined.

METHODS

Twenty-eight Dutch rabbits weighing between 1.5 and 3.2 kg were studied. Sixteen were used in physiological measurements of respiration and 12 in the studies of blood-gas tensions.

Tidal volume, respiratory frequency and minute volume were measured in the conscious rabbit using a face-mask, one-way valve system and pneumotachograph (Khanna and Pleuvry, 1978). After each experimental session the apparatus was calibrated for tidal volume using a small animal ventilator set at appropriate respiratory frequencies.

Rabbits were placed in an adjustable restraining box with the head projecting through a circular orifice. A 25-gauge Butterfly needle was inserted into a lateral ear vein. After stable recordings were obtained the rabbit was given saline, a selected dose of fentanyl or R 39209. As far as possible each rabbit was allocated a single dose of fentanyl, R 39209 or saline on a random basis so that no rabbit received the same dose of drug twice. Rabbits were not used more frequently than at 2-week intervals. The injection was given over a

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0007–0912/80/111101-06 $01.00

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period of 60–75 s to minimize the risk of convulsion. Continuous recordings were taken for at least 15 min after injection.

$P\text{CO}_2$ and pH measurements were determined (Radiometer micro system (BMS3 Mk 2)) using arterialized venous blood from a lateral ear vein collected in heparinized capillary tubes (Khanna and Pleuvry, 1978). Standard bicarbonate was calculated using a Siggaard–Andersen nomogram assuming a normal haemoglobin concentration. The ears were kept warm throughout the sampling period by proximity to an electric light. Under control conditions, $P\text{O}_2$ of blood obtained by this method was 13.21 ± 0.13 kPa ($n = 57$).

Constant temperature and humidity were maintained in the operating theatre throughout each investigation. All injections, recordings and blood sampling were performed by the same person (J.H.B.) and the blood-gas analyser was operated by the same assistant.

The results obtained from the pneumotachograph trace are expressed as a percentage change from pre-injection values, whereas blood-gas results are expressed as absolute change. Significance was assessed using Student's *t* test.

Repeated injections were given at regular intervals corresponding to the time-course of the drug: 10 min for R 39209 and 15 min for fentanyl. Four separate doses were given, and continuous recordings taken for 40 min and 60 min respectively. Control rabbits were given saline repeatedly.

Drugs and doses

The drugs used were R 39209 2, 4, 6, 8 and 10 μg kg^{-1}, and fentanyl 1.25, 2.5 and 5 μg kg^{-1}. Studies using repeated injections were confined to R 39209 6 μg kg^{-1} given at 10-min intervals and fentanyl 2.5 μg kg^{-1} given at 15-min intervals.

RESULTS

Single injections

Both R 39209 and fentanyl produced dose-dependent changes in respiratory frequency and minute volume. The maximum depression of respiratory frequency after the injection of R 39209 occurred earlier than that of fentanyl ($P < 0.01$: Mann–Whitney U test). The peak effect in most rabbits given R 39209 was at 3 min, whilst that for fentanyl was at 5 min. Accordingly, the means for each dose at these respective times were used to calculate the dose–response curves (fig. 2). R 39209 2 μg kg^{-1} had no significant effect, but 4 μg kg^{-1} produced significant decreases in respiratory frequency for up to 5 min. There were significant decreases in both respiratory frequency and minute volume for up to 5 min

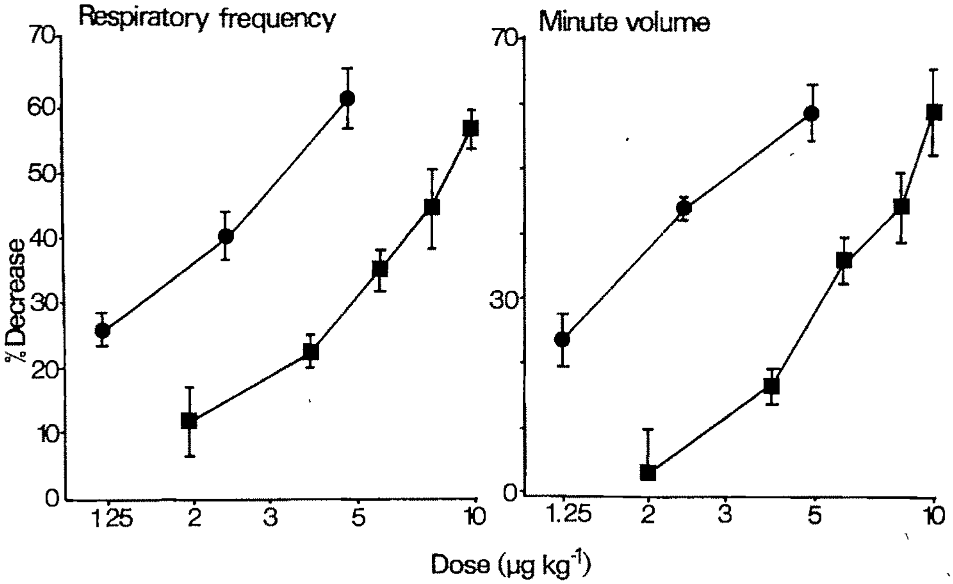

FIG. 2. Dose–response curves for the effect of fentanyl (●) and R 39209 (■) on respiratory frequency and minute volume in the rabbit. Results are expressed as mean maximum percentage decrease (±SEM) of four to eight experiments

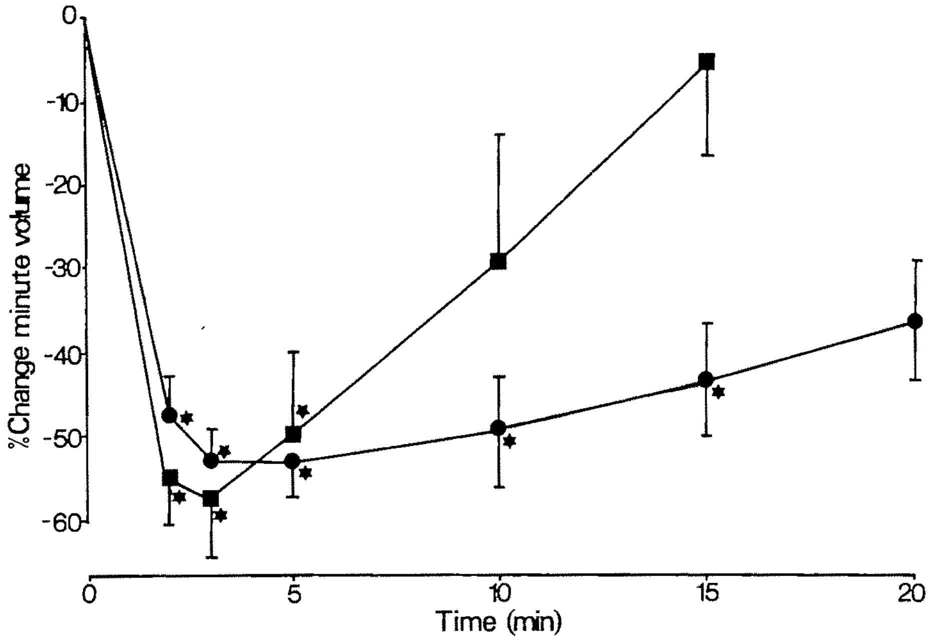

FIG. 3. Time-courses of the effects of fentanyl 5 μg kg^{-1} (●) and R 39209 10 μg kg^{-1} (■) on the minute volume of the rabbit. Results are expressed as mean percentage change (±SEM) from pre-drug values ($n = 4$). *Significantly different from saline control values ($P < 0.05$).

following 6, 8 and 10 μg kg^{-1}. Greater doses of R 39209 invariably produced convulsions and even 8 and 10 μg kg^{-1} produced fatal convulsions if injected rapidly.

Fentanyl 1.25 μg kg^{-1} caused some significant decreases in respiratory frequency and minute volume for up to 10 min, as did 2.5 and 5 μg kg^{-1} for up to 15 min. The time course of the effects of R 39209 10 μg kg^{-1} and fentanyl 5 μg kg^{-1} on minute volume are illustrated in figure 3 and the longer duration of action of fentanyl demonstrated.

The changes in $P\text{CO}_2$ after R 39209 2, 6 and 10 μg kg^{-1} (table I) were significant up to 5 min after injection, but had returned to control values by 10 min. Fentanyl also produced significant increases in $P\text{CO}_2$ which took 20 min to return to control values following both doses. The concur-

TABLE I. *Changes in blood* $P\text{CO}_2$ *(kPa) after single injections of fentanyl and R 39209 (mean ± SEM). *Significantly different from saline* ($P < 0.05$)

	Fentanyl (μg kg^{-1})		R 39209 (μg kg^{-1})			
	2.5	5	2	6	10	Saline
n	5	5	6	14	5	6
Pre-injection	3.89±0.08	4.01±0.11	3.98±0.10	3.81±0.04	4.05±0.15	3.88±0.07
Post-injection						
2 min	+0.96±0.20*	+0.61±0.17*	+0.44±0.08*	−0.39±0.14*	+1.20±0.21*	−0.09±0.12
3 min	+0.78±0.08*	+0.53±0.20*	+0.17±0.07*	−0.42±0.12*	+0.57±0.17*	−0.13±0.09
5 min	+0.67±0.13*	+0.60±0.14*	+0.18±0.13	+0.38±0.10*	+0.69±0.09*	−0.18±0.08
10 min	+0.54±0.13*	+0.64±0.10*	−0.05±0.07	+0.05±0.08	+0.21±0.11	−0.18±0.16
15 min	+0.54±0.14*	+0.78±0.09*	+0.11±0.11	+0.05±0.08	+0.08±0.11	+0.14±0.16
20 min	+0.49±0.14	+0.68±0.25	+0.09±0.13	+0.19±0.09	+0.14±0.10	—

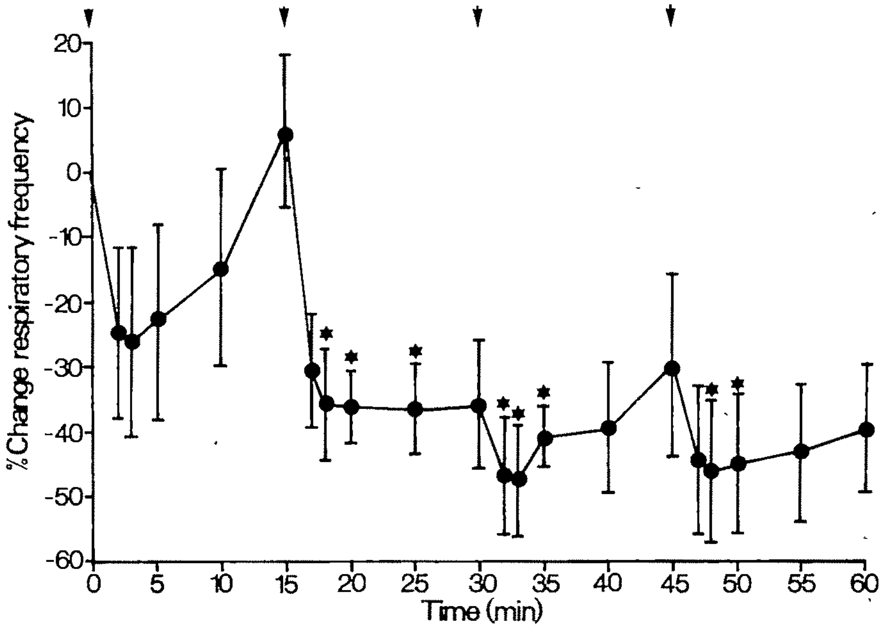

FIG. 4. Effect of repeated injections of fentanyl 2.5 μg kg^{-1} on the respiratory frequency of the rabbit. Fentanyl was injected at 15-min intervals. Results are expressed as mean percentage change (±SEM) from pre-drug values ($n = 4$). *Significantly different from control animals given repeated injections of saline ($P < 0.05$).

rent decrease in pH showed a similar pattern. No significant changes in standard bicarbonate were obtained with any single injection of either drug.

Repeat injections

Fentanyl produced a stepwise decrease in respiratory frequency throughout the 60-min period (fig. 4). However, there was a progressive increase in tidal volume such that the changes in minute volume were not significantly different from those of the saline controls.

R 39209 showed more distinct and regular changes in respiratory frequency (fig. 5). In contrast to fentanyl, tidal volume decreased slightly over the 40-min period, and the time-course of the changes in minute volume resembled closely that of respiratory frequency.

Saline controls showed a gradual decrease in respiratory frequency over 60 min (e.g. decrease of 16.7% (SEM ± 3.92) at 60 min).

Maximum changes in $P\text{CO}_2$ after repeat injections of both R 39209 and fentanyl are shown in table II; the effect was reproducible. However, by the third and fourth doses the $P\text{CO}_2$ had not returned to control values before the next injection (table III).

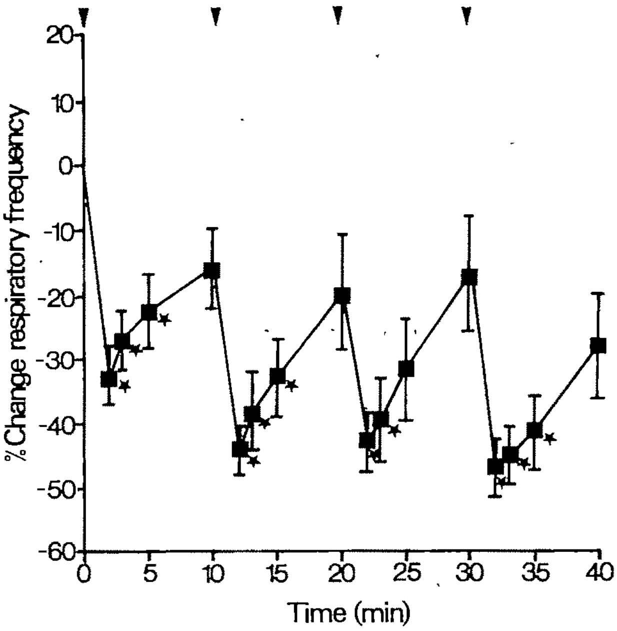

FIG. 5. Effect of repeated injections of R 39209 6 μg kg^{-1} on the respiratory frequency of the rabbit. R 39209 was injected at 10-min intervals. Results are expressed as mean percentage change (±SEM) from pre-drug values ($n = 7$). *Significantly different from control animals given repeated injections of saline ($P < 0.05$).

TABLE II. *Maximum change in blood* P_{CO_2} *(kPa) after repeated injections of fentanyl or R 39209. Results are mean change from control (±SEM) (n = 5). *Values significantly different from saline* ($P < 0.05$)

	Fentanyl 2.5 μg kg^{-1}	R 39209 6 μg kg^{-1}	Saline
Before drug	3.87±0.12	3.73±0.09	4.03±0.16
After drug			
Dose 1	+0.82±0.11	+0.74±0.10	+0.39±0.30
Dose 2	+0.84±0.10*	+0.63±0.06*	0.00±0.24
Dose 3	+0.93±0.33*	+0.55±0.06*	−0.10±0.18
Dose 4	+0.63±0.12*	+0.59±0.13*	−0.01±0.19

TABLE III. *Blood* P_{CO_2} *before each repeat injection of fentanyl or R 39209. Results are mean change from pre-drug control (±SEM)* (n = 5). *(Dose 5 was hypothetical)*

	Fentanyl 2.5 μg kg^{-1}	R 39209 6 μg kg^{-1}	Saline
Before			
Dose 1	0	0	0
Dose 2	+0.22±0.24	+0.22±0.12	+0.01±0.09
Dose 3	+0.33±0.05	+0.53±0.09	+0.21±0.16
Dose 4	+0.53±0.24	+0.32±0.04	+0.04±0.14
Dose 5	+0.49±0.14	+0.40±0.21	+0.10±0.13

R 39209 showed a distinct pattern of change in pH which did return to pre-injection values after each 10-min period.

Neither saline nor fentanyl produced significant changes from their pre-injection values in standard bicarbonate (paired *t* test). However, after the second dose of R 39209, the rabbits exhibited an increase in standard bicarbonate which was significant ($P < 0.05$) for most of the experimental period. For example, 40 min after the beginning of the experiment, rabbits treated with R 39209 had increases in standard bicarbonate of +1.42 (SEM±0.36) mmol litre^{-1} compared with saline control values of −0.36 (SEM ± 0.54) mmol litre^{-1}.

DISCUSSION

The potency ratio between fentanyl and R 39209 varied from 2 : 1 with the higher doses to 3.5 : 1 with the lower doses (fig. 2). Since previous studies (Janssen preclinical research report) of the analgesic effects of R 39209 in rats and dogs had shown fentanyl to have four times the potency of R 39209, it may be that the potency ratio for respiratory effects differs from that for analgesia, or that the assessment of respiratory effects is more sensitive than the methods used for estimating analgesia.

The peak effects of R 39209 on respiratory frequency and minute volume occurred 1–2 min before those of fentanyl and its duration of action was less than half that of fentanyl. With these two exceptions, the respiratory effects of R 39209 were qualitatively indistinguishable from those of fentanyl.

Since blood P_{CO_2} is changed relatively slowly by respiratory depression (for example, apnoea produces an increase in P_{CO_2} of less than 0.5 kPa min^{-1} (Frumin, Epstein and Cohen, 1959; Eger and Severinghaus, 1961)), the changes in P_{CO_2} were found to be less helpful than the changes in minute volume and respiratory frequency when examining the respiratory effects of ultra short-acting drugs.

The effects of repeated injections of either fentanyl or R 39209 were remarkably reproducible as regards maximum effects. However, with successive doses of these drugs, there was a tendency for the control values not to be regained within the 10- or 15-min period (fig. 4, table III). This could indicate cumulation, but it is possible also that the drugs possess sedative effects which reduced the excitability of the rabbits. In this connection, it was observed that the rabbits given R 39209 in doses of 6 μg kg^{-1} and more were more tranquil than those given either saline or fentanyl. Only rarely did they attempt to wriggle free of the mask, an activity which was frequent in saline-treated rabbits. An association between R 39209 and tranquillity in the period after surgery was noted during clinical studies (De Castro, 1977).

This investigation has shown that R 39209 can be given safely to spontaneously breathing rabbits. In view of its evanescent effect, it may have clinical advantages for spontaneously breathing humans who are undergoing transient yet acutely painful procedures such as manipulation of fractures, dilatation and curettage and conservation dentistry. This study in rabbits has shown also that repeated injections may be given with reproducible effects. However, the time-course must first be evaluated in man and safe time intervals for repeated injections determined.

Note added in proof· R 39209 is now known as alfentanyl.

ACKNOWLEDGEMENTS

The authors are indebted to Miss Stephanie Maddison for invaluable technical assistance and to Janssen Pharmaceutical Limited for supplies of R 39209 and some financial assistance with this project.

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EFFETS RESPIRATOIRES D'UN NOUVEL ANALGESIQUE OPIACE: LE R 39209, SUR LE LAPIN: COMPARAISON AVEC LE FENTANYL

RESUME

On a fait sur des lapins une étude sur les effets respiratoires d'un nouvel analgésique de courte durée, R 39209, et on a comparé les résultats obtenus avec ceux du fentanyl. On a mesuré le débit cardiaque, la fréquence respiratoire, le pH, la Pco_2 et le bicarbonate du sang veineux artérialisé. R 39209 a eu un effet de pointe plus rapide et de plus courte durée que le fentanyl, mais autrement les deux médicaments ont eu des effets respiratoires similaires Le fentanyl a été entre 2 et 3,5 fois plus actif que le R 39209. Des doses répétées de R 39209 ont causé des effets de pointe reproductibles, même lorsqu'on n'a laissé que 10 min entre chaque administration.

RESPIRATORISCHE EFFEKTE DES NEUEN, OPIUMHÄLTIGEN ANALGESIEMITTELS R 39209 IM KANINCHEN: VERGLEICH MIT FENTANYL

ZUSAMMENFASSUNG

Die respiratorischen Effekte von R 39209, einem neuen, kurzwirkendem Schmerzlinderungsmittel, wurden bei Kaninchen studiert und mit denen von Fentanyl verglichen. Minutenvolumen, Atmungsfrequenz, pH, Pco_2 und Standard-Bicarbonat des arterialisierten venosen Blutes wurden gemessen. R 39209 hatte eine fruhere Spitzenwirkung und eine kürzere Wirkungsdauer als Fentanyl, ansonsten waren die respiratorischen Effekte der beiden Drogen ahnlich. Fentanyl war zwischen 2 und 3,5 mal stärker als R 39209. Wiederholte Dosen von R 39209 ergaben reproduzierbare Spitzenwirkungen, auch wenn die Verabreichungen nur in Anstanden von 10 Minuten erfolgten.

EFFECTOS RESPIRATORIOS DE UN NUEVO OPIATO ANALGESICO, R 39209, EN EL CONEJO: COMPARACION CON EL FENTANIL

SUMARIO

Se estudiaron en el conejo los efectos respiratorios del R 39209, un nuevo analgesico de corta duración, y se compararon con los del fentanil. Se midió el volumen por minuto, la frecuencia respiratoria y el pH, el Pco_2 y el bicarbonato típico existente en la sangre venosa oxigenada. El R 39209 mostró un efecto de cresta más temprano y una acción de menor duración que el fentanil, pero en lo demás los efectos respiratorios de ambas drogas fueron similares. El fentanil fue de 2 a 3,5 veces más potente que el R 39209. Repetidas dosis de R 39209 produjeron efectos de cresta reproductibles, incluso cuando se dejó transcurrir un lapsus de tan sólo 10 min entre sucesivas administraciones.

Br. J. Anaesth. (1980), 52, 1107

ANALGESIC EFFECT OF APROTININ IN THE RAT AND ITS INHIBITION BY NALOXONE

G. P. NOVELLI, E. PIERACCIOLI, V. A. PEDUTO AND F. FESTIMANNI

SUMMARY

Experiments were performed on rats using two analgesimetric tests (tail-flick; hot-plate) before and after injection i.v. of graded doses of aprotinin (12.5, 25 0 and 50 KIU g^{-1}). A dose-related analgesic effect was noted with both tests. Prior administration of naloxone 0.001 mg g^{-1} i.p. inhibited the analgesic action.

Aprotinin, a polypeptide composed of 58 amino acids (molecular weight 6512) is a broad-spectrum inhibitor of proteases, used clinically in the treatment of coagulation disorders, shock and acute pancreatitis. It is measured as kallikrein inhibiting units (KIU).

During clinical investigations on the management of pain it was noted unexpectedly that aprotinin 500 000–800 000 KIU administered as an i.v. infusion decreased surgical (Novelli et al., 1978; Casali, Marsili and Novelli, 1979) and traumatic pain (De Gaudio, Peli and Muncibi, 1978). This unexpected analgesic effect, although definite and well documented, was observed in patients during the period after operation and could be subject, therefore, to criticism because of the psychological factors that may influence clinical studies.

Therefore, the analgesic actions of aprotinin were studied in rats submitted to standard, quantitative analgesimetric tests and the dose–effect relationship between aprotinin and analgesia was investigated.

METHODS

Experiments were performed on male Wistar rats (weighing 200 ± 10 g) which were caged uniformly and given a standard balanced diet. The analgesic effects were measured using the tail-flick test (Socrel analgesimeter) (D'Armour and Smith, 1941) and the hot-plate test (Wolfe and MacDonald, 1944). The animals were studied in a quiet, semi-dark room to exclude environmental factors, and at the same time of day so that the circadian rhythm of opiate polypeptides (Frederickson, 1977) could be maintained.

Aprotinin (Kir, Richter) was administered in 1 ml of physiological saline into a tail vein and naloxone hydrochloride (Narcan, Endo) 0.001 mg g^{-1} was given i.p. This dose is the minimum effective in precipitating immediate abstinence signs after acute narcotic medication in the rat (Teiger, 1974).

Aprotinin was given in doses of 12.5 KIU g^{-1} i.v. (15 rats), 25 KIU g^{-1} i.v. (30 rats) and 50 KIU g^{-1} i.v. (30 rats). Paired measurements of pain threshold were performed using the tail-flick test before the injection and again 10, 15, 20, 25 and 30 min afterwards. In addition, paired measurements of pain threshold were performed using the hot-plate test before the administration of aprotinin 50 KIU g^{-1} (20 rats) and 10, 15, 20, 25 and 30 min afterwards. The effect of aprotinin on the pain threshold was determined as follows: (a) before treatment with naloxone; (b) 10 min after naloxone 0.001 mg g^{-1} i.p.; (c) 10, 15 and 20 min following aprotinin 50 KIU g^{-1} injected 15 min after naloxone. Paired measurements of pain threshold were obtained using the tail-flick (18 rats) and hot-plate tests (10 rats).

Student's *t* test was used to compare the results obtained before the administration of aprotinin with those determined, at various time intervals, after injection.

RESULTS

The smallest dose of aprotinin did not show any significant analgesic effect but the larger doses prolonged the tail-flick latency in a dose-related manner (fig. 1). The duration of analgesia was also dose-related: the effects of aprotinin 50 KIU g^{-1} were still significant 25 min after injection (table I).

Naloxone, by itself, lowers the pain threshold (Jacob, Tremblay and Colombel, 1974). Similar

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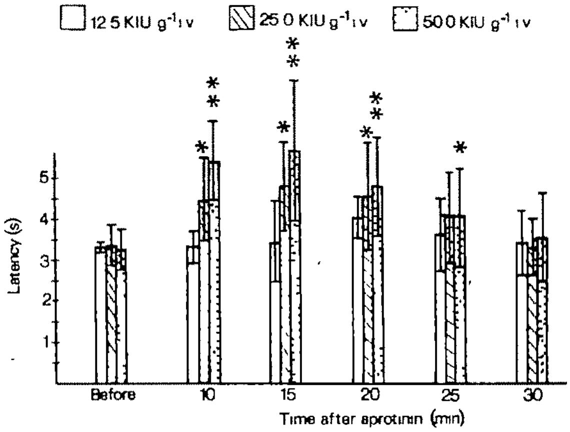

FIG. 1. Analgesic effects of various doses of aprotinin i.v. as measured by tail-flick test. *$P<0.05$; **$P<0.01$.

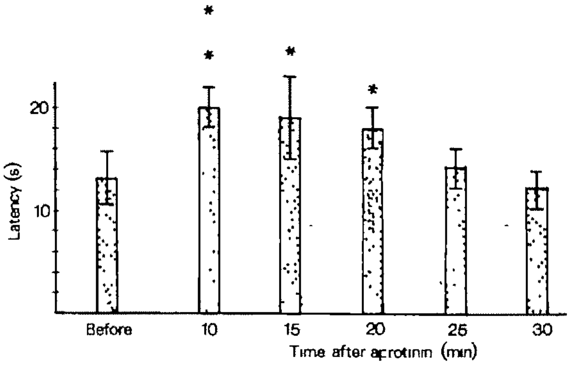

FIG. 2. Analgesic effects of aprotinin 50 KIU g^{-1} as measured by hot-plate test. *$P<0.05$; **$P<0.01$.

results were obtained using the hot-plate test (table II, fig. 2). The administration of naloxone inhibited the analgesic effects of aprotinin (table III, figs 3, 4).

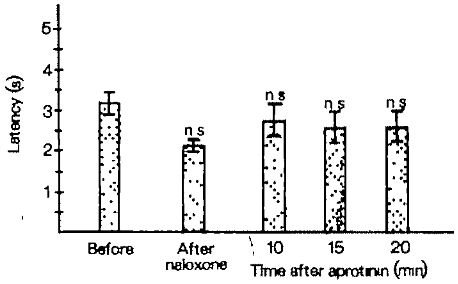

FIG. 3. Inhibition by naloxone of analgesic effect of aprotinin 50 KIU g^{-1} as measured by tail-flick test.

DISCUSSION

The evidence of an analgesic effect of aprotinin is confirmed by the present data. Previously, we administered aprotinin 500 000 KIU by i.v. infusion to surgical patients over 1 h and found that it was as potent as acetylsalicylic acid 1500 mg and that its effect lasted 1–2 h. However, the dose of aprotinin used in these animal experiments cannot be related to those administered clinically because the experimental methods used to study pain threshold cannot be compared to pain after operation and the methods of administration of aprotinin were different in rats and in men.

TABLE I. *Pain threshold as measured by tail-flick test following the injection of aprotinin i.v.*

Test	Number of rats	Control (s)	Aprotinin (KIU g^{-1})	Reaction time after aprotinin (s)				
				10	15	20	25	30
Tail-flick	15	3.31±0.14	12.5	3.38±0.37 n.s.	3.39±1.05 n.s.	4.05±0.47 n.s.	3.64±0.89 n.s.	3.41±0.81 n.s.
Tail-flick	30	3.34±0.57	25.0	4.43±0.96 $P<0.05$	4.74±1.15 $P<0.05$	4.47±1.14 $P<0.05$	4.00±1.08 n.s.	3.26±0.72 n.s.
Tail-flick	30	3.28±0.55	50.0	5.37±1.09 $P<0.001$	5.61±1.71 $P<0.01$	4.76±1.22 $P<0.01$	3.99±1.27 $P<0.05$	3.53±1.11 n.s.

TABLE II *Pain threshold as measured by hot-plate test following aprotinin 50 KIU g^{-1} i.v.*

Test	Number of rats	Control (s)	Reaction time after aprotinin (s)				
			10	15	20	25	30
Hot-plate (52 °C)	20	13.20±2.71	20.00±2.09 $P<0.01$	18.80±4.01 $P<0.05$	18.20±2.03 $P<0.05$	14.00±2.09 n.s.	11.80±1.83 n.s.

TABLE III. *Pain threshold as measured by two analgesimetric tests before and after aprotinin 50 KIU g^{-1} i.v. following naloxone 0.001 mg g^{-1} i.p*

Test	Number of rats	Control (s)	Reaction time after naloxone (s)	Reaction time after aprotinin (s)		
				10	15	20
Tail-flick	18	3.23±0.32	2.14±0.11 n.s.	2.76±0.44 n.s.	2.63±0.37 n.s.	2.64±0.40 n.s.
Hot-plate	18	13.83±2.47	11.33±0.48 n.s.	10.66±1.02 n.s.	11.32±0.88 n.s.	10.33±0.69 n.s.

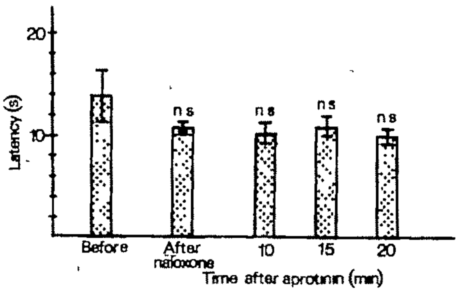

FIG. 4. Inhibition by naloxone of analgesic effect of aprotinin 50 KIU g^{-1} as measured by hot plate-test.

Nevertheless, the primary aim of the present experiments was to demonstrate the analgesic action of the protease inhibitory drug.

The uniformity of the data obtained using two different experimental analgesimetric tests, each one expressing a different level of sensory integration, is remarkable and the inhibition of the analgesic action by naloxone suggests that there has been interference in the neurotransmission and neuromodulation of endogenous opiate polypeptides. The exact site of this interference is not clear, but it seems to be related to an action on the central nervous system as indicated by Bertolini, Genedani and Castelli (1977) who provoked analgesia in the rat by injecting aprotinin to the lateral ventricle.

Since protease inhibition should decrease the formation of the opioid polypeptides from the beta-lipotropin amino acid long chain, hyperalgesia should be observed.

The most likely hypothesis to explain the analgesic action is an inhibition of the hydrolytic breakdown of endogenous opioid polypeptides which would increase the concentration and duration of action of endogenous opioid polypeptides on the specific receptors. Another possible hypothesis is that an endorphin-like peptide is formed during the metabolic breakdown of aprotinin. Although the results do not explain the mechanism of the analgesic effects of aprotinin, they may shed light on the mechanisms of "physiological analgesia".

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EFFET ANALGESIQUE DE L'APROTININE CHEZ LE RAT ET SON INHIBITION PAR LE NAXOLONE

RESUME

Des expériences ont été réalisées chez des rats au moyen de deux essais analgesimétriques (frémissements de la queue; plaque chauffante) avant et aprés l'injection i.v. de doses graduées d'aprotinine (12,5, 25,0 et 50 KIU g^{-1}). On observa dans les deux essais un effet analgésique en fonction de la dose. L'administration préalable de 0,001 mg g^{-1} i.p. de naxolone inhiba l'action analgésique.

SCHMERZLINDERNDE WIRKUNGEN VON APROTININ BEI DER RATTE UND IHRE UNTERDRÜCKUNGDURCH NALOXON

ZUSAMMENFASSUNG

Es wurden Experimente mit Ratten unternommen, bei denen zwei analgesimetrische Tests (Schwanzschlag; warmer Teller) vor und nach der intravenösen Verabreichung von abgestuften Dosen von Aprotinin (12,5 25,0 und 50 KIU g^{-1}) verwendet wurden. Eine dosisbezogene schmerzlindernde Wirkung wurde bei beiden Tests festgestellt. Durch vorherige Verabreichung i.p. von Naloxon 0,001 mg $^{-1}$ konnte diese schmerzlindernde Wirkung unterdrückt werden.

EFECTO ANALGESICO DEL APROTININ EN LA RATA Y SU INHIBICION MEDIANTE NALOXONA

SUMARIO

Se llevaron a cabo experimentos en ratas usando dos pruebas analgesimétricas (movimiento de cola y plancha caliente) antes y después de la inyección intravenosa de dosis regularizadas de aprotinin (12,5, 25,0 y 50 KIU g^{-1} (unidades inhibidoras de Kallikrein). En ambas pruebas se apreció un efecto analgésico relacionado a la dosis. El haber administrado 0,001 mg g^{-1} de naloxona con anterioridad inhibió la acción analgésica.

Br. J. Anaesth. (1980), 52, 1111

DIFFERENTIAL EFFECTS OF MYONEURAL BLOCKING DRUGS ON NEUROMUSCULAR TRANSMISSION

N. E. WILLIAMS, S. N. WEBB AND T. N. CALVEY

SUMMARY

The relationship between the depression in the amplitude of the compound muscle action potential and neuromuscular decrement (fade) was studied during the induction of non-depolarizing blockade, using a train of four supramaximal stimuli. Neuromuscular decrement (%) was defined as: $\{1-(\text{amplitude of fourth muscle action potential})/(\text{amplitude of first muscle action potential})\} \times 100$ When the amplitude of the first action potential was reduced by 50%, mean neuromuscular decrement increased in the order pancuronium < alcuronium < tubocurarine < fazadinium < gallamine. Similarly, the slope of the regression line relating the decrease in the amplitude of the action potential to decrement was least with pancuronium and greatest with gallamine. These results may reflect different affinities or intrinsic activities of the five drugs for prejunctional and postjunctional receptors. Thus, pancuronium may have a greater affinity for postsynaptic receptors, while tubocurarine and gallamine affect selectively the motor nerve terminal. It was confirmed that fazadinium had a more rapid onset of action than any of the other myoneural blocking drugs studied.

Current evidence suggests that tubocurarine impairs neuromuscular transmission at both presynaptic and postsynaptic sites in the region of the motor endplate. While it has been accepted for many years that the drug competes with acetylcholine for receptors on the postsynaptic membrane (Dale, Feldberg and Vogt, 1936; Fatt and Katz, 1952), more recent evidence has shown that the excitability of the motor nerve terminal is depressed also, resulting in a decrease in the release of the neurotransmitter (Riker, 1966; Galindo, 1972). The relative importance of these effects is a matter of controversy, and little is known of their role in the production of neuromuscular blockade in man.

When non-depolarizing neuromuscular blockade is induced in clinical anaesthesia, characteristic effects on the e.m.g. or the muscle twitch are observed. The amplitude of the compound muscle action potential or the muscle twitch is decreased, and there is considerable decrement (fade) between the successive responses elicited by repetitive nerve stimulation. Both these phenomena can be interpreted in terms of competition between the myoneural blocking drug and acetylcholine for (a) presynaptic receptors (b) postsynaptic receptors or (c) both presynaptic and postsynaptic receptors in the region of the neuromuscular junction. The present experiments were designed to determine if the myoneural blockers in current clinical use have single or multiple sites of action at the neuromuscular junction. If all non-depolarizing agents that produce neuromuscular blockade in man have a single site of action (at either prejunctional or postjunctional receptors), the relation between the amplitude of the action potential and decrement should be invariably constant. By contrast, if non-depolarizing agents produce neuromuscular block by both presynaptic and postsynaptic effects, the relation between amplitude and decrement may vary with different drugs (depending on the variable affinity of the drugs for each group of receptors). The relation between the amplitude of the initial action potential and decrement has been studied during the induction of neuromuscular block by five different non-depolarizing agents. The rate of onset of neuromuscular block for each myoneural blocker was investigated also.

PATIENTS AND METHODS

Twenty-five adult patients, of both sexes, were studied during the induction of competitive neuromuscular blockade before operative surgery.

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0007-0912/80/111111-05 $01.00

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Most subjects were premedicated with nitrazepam 10 mg orally, given on the previous night, and diazepam 5–10 mg orally on the day of operation. Anaesthesia was induced with thiopentone 200–400 mg, followed by nitrous oxide 60–70% in oxygen. One forearm was immobilized in a splint and the hand and wrist were prepared for electromyography (Roberts and Wilson, 1969). The ulnar nerve was stimulated percutaneously, using a train of four supramaximal rectangular pulses (4 Hz; 150–175 V; stimulus duration 0.5 ms). Muscle action potentials were recorded from the adductor pollicis by surface electrodes, and the amplitude of each potential was assessed by reference to a standard calibration pulse. After amplification, the potentials were displayed on an oscilloscope and recorded on light-sensitive paper.

After several control recordings, tubocurarine 40–45 mg, pancuronium 5.0–8.0 mg, alcuronium 15–20 mg, gallamine 80–160 mg, or fazadinium 32–75 mg was injected i.v. over a 10-s period and e.m.g. were recorded at 10–15 s intervals for 3–5 min. Intubation of the trachea and controlled ventilation were carried out during this time at the discretion of the anaesthetist. Each drug was investigated in five different patients during the induction of general anaesthesia.

RESULTS

After the injection of the myoneural blocking drug, the amplitude of the first compound action potential in serial e.m.g. was expressed as a percentage of the control amplitude. Electromyographic decrement was assessed from the amplitude of the first and the fourth potentials elicited by each train of stimuli, using the relationship:

decrement (%) = {1 – (amplitude of fourth action potential)/(amplitude of first action potential)} × 100.

The rate of onset of neuromuscular block (as assessed by both diminished amplitude and decrement) was most rapid with tubocurarine and fazadinium. In the case of both these drugs, there was a 50% decrease in the amplitude of the first potential and 50% decrement within 1–1.5 min of injection (table I). Gallamine and alcuronium had a slightly slower onset of action, while pancuronium had the longest latency (2–3 min) before the onset of neuromuscular block (table I). With the exception of gallamine, the latent period required for a 50% reduction in the amplitude of the initial action potential was less than the time required for the corresponding decrease in neuromuscular decrement.

TABLE I. *Time of onset of neuromuscular block. Values represent the mean ± SEM of five results. Neuromuscular decrement (%) was defined as {1 – (amplitude of fourth action potential)/(amplitude of first action potential)} × 100*

Drug	Latent period before 50% decrease in amplitude of first action potential (s)	Latent period before 50% neuromuscular decrement (s)
Tubocurarine	61.8 ± 13.5	82.3 ± 10.0
Pancuronium	130.0 ± 29.8	162.2 ± 20.0
Alcuronium	92.6 ± 15.7	116.6 ± 9.0
Gallamine	106.0 ± 19.2	99.0 ± 25.5
Fazadinium	70.2 ± 9.3	77.2 ± 8.7

The relation between the amplitude of the first compound muscle action potential and neuromuscular decrement was not constant, but varied considerably with each drug (fig. 1). Although there was marked individual variability (fig. 1), when the amplitude of the first potential was reduced by 50%, the mean neuromuscular decrement increased in the order pancuronium < alcuronium < tubocurarine < fazadinium < gallamine. With the exception of alcuronium, this relationship was observed usually at different degrees of neuromuscular blockade (fig. 1). Similarly, despite the considerable individual variability, the mean slope of the regression line relating the decrease in action potential amplitude to neuromuscular decrement in each group of patients was least with pancuronium and greatest with gallamine (pancuronium < alcuronium < fazadinium < tubocurarine < gallamine; table II). Differences between the slopes of the regression lines for each drug were analysed by the unpaired t test; significant differences were observed between the gradients for pancuronium and tubocurarine ($t = 4.692$; $0.01 > P > 0.001$) and pancuronium and gallamine ($t = 2.792$; $0.05 > P > 0.01$). Differences between the slopes of other regression lines were not statistically significant.

DISCUSSION

During the induction of neuromuscular block, the relationship between the amplitude of the action

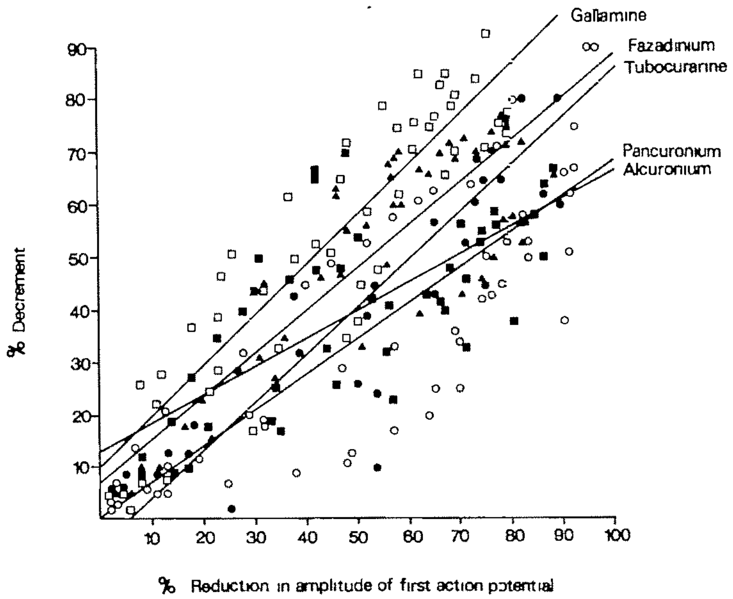

FIG. 1. Relationship between the decrease in amplitude of the first compound muscle action potential and neuromuscular decrement for the five drugs studied. The regression lines represent the relation between these parameters in all the patients studied. ● = tubocurarine; ○ = pancuronium; ■ = alcuronium; □ = gallamine; ▲ = fazadinium.

potential and decrement was not constant, but was affected in a different manner by the five non-depolarizing myoneural blocking drugs. In general, pancuronium and alcuronium reduced preferentially the amplitude of the muscle action potential; tubocurarine and gallamine had more pronounced effects on neuromuscular decrement, while fazadinium influenced both parameters equally. In addition, when pancuronium was compared with tubocurarine or gallamine, there were statistically significant differences in the slope of the regression line relating the decrease in amplitude to neuromuscular decrement.

These results are not consistent with the action of non-depolarizing agents at a single site in the region of the neuromuscular junction. In these conditions, the relationship between the depression in the amplitude of the action potential and decrement at a given degree of neuromuscular block should be constant, and not vary with different drugs. Our present experiments suggest clearly that myoneural blockers paralyse voluntary muscle by acting on more than one group of receptors that are probably located at different sites closely related to the motor end-plate. In recent years, it has been suggested that non-depolarizing blockers impair neuromuscular transmission by acting at both prejunctional and postjunctional receptors (Galindo, 1971, 1972; Bowman and Webb, 1976). The decrease in the

TABLE II. *Relationship between the decrease in amplitude of the first compound muscle action potential and neuromuscular decrement with the five drugs Values represent the slope of the regression line relating the decrease in amplitude to decrement in each of the patients studied*

Patient	Tubocurarine	Pancuronium	Alcuronium	Gallamine	Fazadinium
1	0.9225	0.7026	0.4751	0.9966	0.6298
2	1.2273	0.7759	0.7682	0.9818	1.0066
3	1.0514	0.6723	1.2530	1.4464	0.8938
4	0.9356	0.6920	0.6707	1.5744	1.0042
5	1.1153	0.8549	0.6823	0.8098	0.9603
Mean	1.0504	0.7395	0.7699	1.1618	0.8989
± SEM	0.0570	0.0337	0.1300	0.1475	0.0703

amplitude of the action potential may be mainly a result of postsynaptic receptor blockade; in contrast, the decremental response induced by repetitive nerve stimulation may reflect a decrease in transmitter output, as a result of an effect on the motor nerve terminal (Hubbard and Wilson, 1973). If this interpretation is correct, the five non-depolarizing drugs studied appear to have different affinities or intrinsic activities for prejunctional and postjunctional receptors. Our results may reflect the relative selectivity of pancuronium and alcuronium for postsynaptic receptors, thus reducing preferentially the amplitude of the action potential (Bowman and Webb, 1976); in contrast, gallamine and tubocurarine may have a greater affinity for presynaptic receptors, decreasing the release of acetylcholine by the motor nerve terminal (resulting in decrement). Fazadinium may have an equal affinity and intrinsic activity at both prejunctional and postjunctional receptors. Although these conclusions are necessarily speculative, they are consistent with current views on the mechanism of action of non-depolarizing myoneural blockers.

The present experiments were not designed primarily to assess the rate of onset of neuromuscular block. Nevertheless, our results confirm that fazadinium has a more rapid onset of action than other non-depolarizing drugs (Simpson et al., 1972; Arora et al., 1973), as assessed by the latent period before a 50% decrease in the amplitude of the first action potential or 50% neuromuscular decrement. The dose of fazadinium (approximately 0.5–1.0 mg kg^{-1}) was smaller than that used by other authors, and this probably accounts for the slightly longer latent period (70–80 s) before the onset of neuromuscular block. Tubocurarine had an onset of action similar to that reported by other authors (Blackburn and Morgan, 1978), although the speed of onset of pancuronium was 20–30% longer. These differences are not consistent with previous observations (Harrison, 1972; Blackburn and Morgan, 1978), but may be related to the large scatter of the experimental results or to differences in drug circulation time in the patients studied.

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EFFETS DIFFERENTIELS DE SUBSTANCES DE BLOCAGE MYONEURAL SUR LA TRANSMISSION MUSCULAIRE

RESUME

Au cours de l'induction d'un blocage non dépolarisant réalisé au moyen d'une série de quatre stimulus supramaximaux, on a étudié le rapport entre la dépression de l'amplitude du potentiel d'action musculaire composé et la diminution neuromusculaire (estompage). La diminution neuromusculaire (%) s'établit comme suit: {1 – (amplitude du potentiel d'action du quatrième muscle)/(amplitude du potentiel d'action du premier muscle)} × 100 Lorsque l'on diminuait de 50% l'amplitude du potential d'action première, la diminution neuromusculaire moyenne augmentait dans l'ordre suivant pancuronium < alcuronium < tubocurarine < fazadinium < gallamine. De même, l'inclinaison de la ligne de régression reliant la dépression de l'amplitude du potentiel d'action à la diminution était moins forte avec le pancuronium et plus élevée avec la gallamine Ces résultats reflètent peut-être les diverses affinités ou activités intrinsèques de ces cinq substances vis-à-vis des récepteurs de jonctions antérieurs et postérieurs. Ainsi, le pancuronium a peut-être une plus grande affinité vis-à-vis des récepteurs synaptiques posterieurs tandis que la tubocurarine et la gallamine affectent de manière sélective les terminaux des nerfs moteurs. Il s'est avéré que le fazadinium agit beaucoup plus rapidement que toute autre substance de blocage myoneural étudiée.

DIFFERENTIALWIRKUNGEN VON MYONEURALEN BLOCKIERUNGSMITTELN AUF DIE NEUROMUSKULÄRE ÜBERTRAGUNG

ZUSAMMENFASSUNG

Der Zusammenhang zwischen der Schwächung der Amplitude des Gesamtmuskeltätigkeitspotentials und der neuromuskulären Verminderung (Schwundeffekt) wurde während der Einleitung einer nicht depolarisierenden Blockade studiert, wobei ein Zug von vier supramaximalen Reitzmitteln verwendet wurde. Die neuromuskuläre Verminderung (%) wurde wie folgt definiert: {1 – (Amplitude des vierten Muskeltätigkeitspotentials)/(Amplitude des ersten Muskeltätigkeitspotentials)} × 100. Wenn die Amplitude des ersten Tätigkeitspotentials um 50% reduziert wurde, steigerte sich die durchschnittliche neuromuskulare Verminderung in der Reihenfolge Pancuronium < Alcuronium < Tubocurarin < Fazadinium < Gallamin. Ähnlicherweise war die Neigung der Regressionsgerade, die die Verminderung der Amplitude des Tätigkeitspotentials zu der neuromuskulären Verminderung in Beziehung setzte, bei Pancuronium am schwächsten und bei Gallamin am stärksten. Diese Ergebnisse konnten verschiedene Affinitaten oder wesentliche Tatigkeiten der fünf Mittel für präsynaptische oder postsynaptische Rezeptoren widerspiegeln. Pancuronium könnte also eine stärkere Affinität für postsynaptische Rezeptoren aufweisen, während Tubocurarin und Gallamin selektiv auf des Bewegungsnervende einwirken. Es wurde bestätigt, dass bei Fazadinium die Wirkung viel schneller eintrat als bei den anderen myoneuralen Blockierungsmitteln, die studiert wurden.

EFECTOS DIFERENCIALES DE LAS SUBSTANCIAS BLOQUEADORAS MIONEURALES SOBRE LA TRASMISION NEUROMUSCULAR

SUMARIO

La relación entre la depresión de la amplitud del potencial de acción muscular compuesto y la disminución neuromuscular (desaparición gradual) fue objeto de un estudio bajo inducción de un bloqueo no-depolarizante al usar una serie de cuatro estímulos supramaximos. La disminución neuromuscular (%) se definió de la siguiente manera {1 – (amplitud del cuarto potencial de acción del múscular)/(amplitud del primer potencial de acción del múscular)} × 100. Cuando se redujo la amplitud del primera potencial de acción de un 50%, la disminución neuromuscular media creció en el siguiente orden pancuronio < alcuronio < tubocurarina < fazadinio < galamina. De igual modo, la inclinación de la linea de regresión que relacionaba la depresión de la amplitud del potencial de acción a la disminución era menor con el pancuronio y mayor con la galamina. Estos resultados pueden reflejar afinidades o actividades intrínsecas distintas de las cinco substancias para con los receptores prejuncionales y postjuncionales. Asimismo, el pancuronio puede demostrar una mayor afinidad para los receptores postsinápticos, mientras que la tubocurarina y la galamina afectan de manera selectiva al terminal del nervio motor. Se confirmó que el fazadinio actúa mucho más rápido que cualquiera de las otras substancias bloqueadoras mioneurales estudiadas.

Br. J. Anaesth. (1980), **52**, 1117

SPINAL AND GENERAL ANAESTHESIA IN TOTAL HIP REPLACEMENT: FREQUENCY OF DEEP VEIN THROMBOSIS

J. THORBURN, J. R. LOUDEN AND R. VALLANCE

SUMMARY

Subarachnoid block (SAB) or general anaesthesia (GA) was induced in 85 patients undergoing total hip replacement. The frequency of deep vein thrombosis (DVT), assessed by fibrinogen uptake studies and venography, was 29% in those patients receiving SAB and 54% in the GA group Total blood loss (intra-operative and post-operative wound suction drainage) in SAB group was 66% and total transfusion volume 52% of that of GA group. No morbidity attributable to SAB or to the associated arterial hypotension was detected.

The frequency of total hip arthroplasty is increasing steadily in the U.K., and is likely to increase further (Morris, 1975). The operation is associated with a high frequency of deep venous thrombosis (DVT) (Kakkar et al., 1972) and considerable blood loss (Murray, 1973). Prophylaxis against DVT has been disappointingly ineffective, and has produced conflicting results (Kakkar et al., 1972; Hampson et al., 1974; Morris, Henry and Prestow, 1974; Rogers et al., 1978). However, blood loss during operation is decreased following subarachnoid block (SAB) (Sculco and Ranawat, 1975), and general anaesthesia (GA) with induced arterial hypotension (Davis, Jennings and Harris, 1974; Lawson et al., 1976).

This study was undertaken to compare the effects of SAB associated with moderate hypotension with those of GA, on the frequency of DVT, blood loss and transfusion volumes and to detect any morbidity attributable to SAB.

PATIENTS AND METHODS

Eighty-five patients undergoing total hip replacement were studied. Forty-three received general anaesthesia, and 38 spinal anaesthesia. Patients suffering from thyroid disease, taking oral anti-coagulants or with a neurological spinal disease were excluded from the study.

Assessment before operation included physical examination, e.c.g., chest x-ray, determination of haemoglobin concentration and full blood count. The concentrations of the serum electrolytes, urea and creatinine were measured also. The allocation of the patient to receive SAB or GA was dictated by the time available, as SAB took longer to induce than GA. No other factor influenced the selection of patients.

Patients receiving spinal anaesthesia were premedicated with nitrazepam 5–10 mg orally 90 min, and morphine 7.5–15 mg i.m. 60 min before operation. The spinal puncture was made with the patient lying in the lateral position, on the affected hip. A 25-gauge spinal needle was inserted into the subarachnoid space and 2.3–3.0 ml of cinchocaine 0.5% in 6% dextrose (heavy nupercaine) was injected slowly. The lateral position was maintained for 5 min and then changed to supine. If necessary, diazepam was injected i.v. to produce a state of sedation in which the patient was drowsy but rousable.

Patients in the general anaesthetic group were premedicated with morphine 7.5–15.0 mg and atropine 0.6 mg 60 min before operation. Anaesthesia, induced with thiopentone, was maintained with nitrous oxide in oxygen. Following neuromuscular blockade the trachea was intubated and the lungs ventilated mechanically. Deliberate hypotension was not induced. During the operation e.c.g. and heart rate were monitored continuously and the arterial pressure measured intermittently using an oscillotonometer. Blood loss was measured gravimetrically and the volume of blood in the suction jars added to the estimate. The volume of blood transfused to each patient was noted.

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0007–0912/80/111117–05 $01.00

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The volume of blood in the wound suction drain was noted, and the drain was removed 48 h after operation. The haemoglobin concentration was measured on the 3rd day after operation and again before discharge from the orthopaedic unit, approximately 21 days after operation. The volume of blood transfused and the number of patients receiving a transfusion were noted. The greatest serum creatinine concentration after operation was taken as the "post-operative" value (table IV), and the frequency and type of difficulty of micturition noted.

Investigations for the detection of DVT were performed as described by Louden and colleagues (1978). Each patient had a fibrinogen uptake test performed within 2 h of surgery. This was repeated on alternate days and a bilateral ascending venogram performed 6–10 days after operation. DVT was said to be present when a positive fibrinogen uptake test at one or more sites was associated with a venographic abnormality.

Mean arterial pressure was calculated as:

$$\frac{\text{systolic} - \text{diastolic}}{3} + \text{diastolic arterial pressure} = \text{mean mm Hg}$$

The results were analysed using Student's t test or χ^2 test where appropriate.

RESULTS

Approximately two-thirds of the patients were female (table I), but there were no significant differences between the two groups.

TABLE I. *Pre-operative details of the 85 patients (mean ± SEM). There were no significant differences between the groups*

	GA		Spinal	
Number of patients	47		38	
Male	16		11	
Age (yr)	65.6 ±	1.1	64 2 ±	1.5
Haemoglobin (g dl^{-1})	13.5 ±	0.3	13.0 ±	0.3
Mean arterial pressure (mm Hg)	111.7 ±	2.2	112.9 ±	2 1
Serum creatinine (μmol litre^{-1})	90.3 ±	6 8	93.9 ±	5.6
Serum creatinine range (μmol litre^{-1})	38.0 ± 170.0		47.0–226 0	

The blood loss during operation (table II) in the spinal group was 50% of that of GA group and the average mean arterial pressure in the spinal group was reduced from 112 mm Hg to 58 mm Hg during anaesthesia. This represents a mean arterial systolic pressure during blockade of 86 mm Hg. The mean duration of hypotension was 2.5 h. The mean arterial pressure in GA group varied during operation, unlike that of the spinal group.

TABLE II. *Blood loss, mean arterial pressure and blood transfusion during operation (mean ± SEM).* *$P < 0.05$; **$P < 0.005$

	GA	Spinal
Blood loss (ml)	848 ± 61	420.0 ± 40.8*
Mean arterial pressure (mm Hg)	—	58.6 ± 1.4
Volume transfused (ml)	880 ± 60	500.0 ± 0
No. of patients transfused	33 (70%)	4 (10%)**
Number of patients	47	38

Intra-operative blood transfusion was given to four patients in the spinal group (mean volume of 500 ml); 33 patients in GA group received an average of 880 ml of blood (table II). The total volume of blood transfused in SAB group was 52% of that in GA group (table III).

The wound drainage after operation was 558 ml in the spinal group, which was slightly less than that observed in GA group, but the difference was not significant (table III).

The mean haemoglobin concentration was significantly less in the spinal group on the 3rd day after operation by 0.88 g dl^{-1} ($P < 0.05$), but by

TABLE III. *Blood loss, haemoglobin concentration, transfusion volume and serum creatinine concentration after operation (mean ± SEM).* *$P < 0\ 05$

	GA	Spinal
Total patients	47	38
Post-op. drainage (ml)	655.7 ± 38 2	581.6 ± 39
3rd day Hb (g dl^{-1})	11.0 ± 0.3	10.1 ± 0.3*
21st day Hb (g dl^{-1})	10.7 ± 0.3	10.8 ± 0.3
Total vol. transfused (ml)	1345.0 ± 85	930.0 ± 60*
Total patients transfused	39 (82.9%)	22 (57.8%)*
Post-op. serum creatinine (μmol litre^{-1})	102.8 ± 6.8	93.4 ± 8.1*
Creatinine range (μmol litre^{-1})	52–178	40–223

the 3rd week, no difference was observed (table III). A significant difference was observed between the haemoglobin concentrations before and after operation in both groups (table IV).

TABLE IV. *Serum creatinine and haemoglobin concentrations before and after operation* (*mean* ± *SEM*). *P < 0.05; **P < 0.005 (*paired Student's* t *test*)

	GA	Spinal
Number of patients	47	38
Pre-op. serum creatinine (μmol litre^{-1})	90.3 ± 6.8	93.9 ± 5.6
Post-op. serum creatinine (μmol litre^{-1})	102.8 ± 6.8*	93.4 ± 8.0
Pre-op. Hb concentration (g dl^{-1})	13.5 ± 0.3	13.0 ± 0.3
Post-op. Hb concentration (g dl^{-1})		
3rd day	11.0 ± 0.3**	10.1 ± 0.3**
21st day	10.7 ± 0.3**	10.8 ± 0.3**

The serum creatinine concentration after operation was significantly increased in GA group, but no difference between values before and after operation was observed in the spinal group (table IV).

The frequency of difficulties of micturition is shown in table V.

TABLE V. *Frequency and type of micturition difficulties after operation* (*Yates'* χ^2 *test of significance:* *P < 0.05)

	GA	Spinal
Number of patients	47	38
Catheterized	4	7
Carbachol	1	3
Incontinent	5	1
Total problems	10	11

Deep vein thrombosis (DVT) occurred in 11 patients (29%) in the spinal group (table VI) compared with 25 patients (53%) in GA group.

TABLE VI. *Frequency of deep vein thrombosis* (*P < 0.05)

	GA	Spinal
Number of patients	47	38
Number with DVT	25 (53%)	11 (29%)*

DISCUSSION

The results of this study show that SAB was associated with a significant decrease in the frequency of DVT after operation and the volume and frequency of blood transfusion. During surgery, SAB was associated with a significant decrease in the mean arterial pressure, and a 50% decrease in blood loss.

Patients undergoing total hip replacement have the greatest frequency of DVT (Kakkar, 1977) and heparin prophylaxis has produced conflicting results (Kakkar et al., 1972; Hampson et al., 1974; Morris, Henry and Preston, 1974; Rogers et al., 1978). Stamatakis and colleagues (1977) suggested that venous stasis occurring during this type of surgery is an important factor in the causation of DVT and, using intra-operative venography, were able to demonstrate stasis occurring in the leg veins. Blood flow is related to viscosity and the ability of red cells to deform readily during passage through vessels of diameter smaller than themselves. Dr A. Drummond (personal communication) has shown that the ability of red cells to deform is increased during SAB and this may be a factor aiding the increase in limb blood flow observed by Berenyi, Shimasato and Etsten (1964) thus reducing venous stasis and the frequency of DVT.

The total measured blood loss in SAB group was 66% and total transfusion volume 52% of that observed in GA group, but the 21-day haemoglobin concentration was similar in both groups. DVT is associated with red cell consumption, and the increased frequency of DVT occurring in patients receiving general anaesthesia may account for the similar haemoglobin concentration noted in both groups, despite the greater volume of blood received by GA group.

Sculco and Ranawat (1975) compared SAB with GA, and Lawson and colleagues (1976) compared GA plus sodium nitroprusside-induced hypotension with GA, in patients receiving total hip replacement; both groups observed a 50% decrease in blood loss during surgery. The degree of hypotension achieved by Lawson was similar to that occurring in the present study.

Blood loss in this type of surgery is considerable (Murray, 1973) and Landmark and colleagues (1975) have drawn attention to the red cell mass deficit which occurs after operation. In Landmark's study sequential measurements were made of plasma and red cell volumes, and despite clinical and laboratory evidence of adequate blood replacement 2 h after operation, a 24% red cell mass deficit was observed 48 h after surgery. In the present study the haemoglobin concentrations had decreased significantly after operation in both groups of patients.

Patients requiring this type of surgery are usually elderly, and Alexander and Barrow (1978) found the frequency of hypertension to be over 60% in a group of such patients. Patient safety and the use of a hypotensive anaesthetic technique in this group of patients has been questioned by Dennison (1979). In the present series, the patients in the spinal group, although drowsy, could communicate with the anaesthetist if disagreeable subjective sensations were experienced. No clinical evidence of cerebral dysfunction was observed and there were no abnormalities in the e.c.g. No patients in the spinal group developed cardiac or cerebral complications after operation.

If the arterial hypotension associated with SAB jeopardized organ function, this might be reflected in changes in renal function. No significant difference was observed between serum creatinine concentrations before and after operation (table IV) in the spinal group, but a significant increase was observed in GA group. This evidence would suggest that renal function was not impaired by SAB.

On this evidence spinal anaesthesia offers considerable advantages over general anaesthesia by decreasing the frequency of DVT, blood loss and requirements for blood transfusion. No morbidity associated with the technique was observed; indeed there was evidence to suggest that renal function may have been impaired slightly following general anaesthesia.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the help and encouragement of Professor D. Hamblin and Mr J. Graham of the Orthopaedic Division of the Western Infirmary and the secretarial assistance of Miss E. Palfreman.

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ANESTHESIE GENERALE ET RACHIANESTHESIE POUR UN REMPLACEMENT TOTAL DE LA HANCHE FREQUENCE DE LA THROMBOSE PROFONDE DE LA VEINE

RESUME

Le blocage sous-arachnoide (SAB) ou l'anesthésie générale (GA) ont été induits à 85 patients devant subir un remplacement total de la hanche. La fréquence de thrombose profonde de la veine (DVT), évaluée par des études sur la fixation des fibrinogènes et par veinographie, a été de 29% chez les patients ayant reçu la SAB et de 54% pour le groupe GA La perte de sang totale (par drainage par suction de la blessure intra-opératoire et post-opératoire) dans le groupe SAB a été de 66%, et le volume de transfusion totale 52% de celui du groupe GA On n'a constaté aucune morbidité attribuable au SAB ou aucune hypotension artérielle qui pourrait lui être associée.

SPINALE UND ALLGEMEINE NARKOSE BEI VÖLLIGER HÜFTERNEUERUNG: HÄUFIGKEIT VON TIEFER VENENTHROMBOSE

ZUSAMMENFASSUNG

Subarachnoidale Blockierung (SAB) oder allgemeine Narkose (GA) wurde bei 85 Patienten bei totaler Hufterneuerung bewirkt. Die Haufigkeit von tiefer Venenthrombose (DVT), beurteilt durch Untersuchen der Fibrinogenaufnahme und durch Venographie, betrug 29% bei Patienten, die SAB erhielten, und 54% in der GA-Gruppe Der gesamte Blutverlust (Wundabsaugung wahrend und nach der Operation) betrug in der SAB-Gruppe 66%, und das gesamte Transfusionsvolumen 52% der GA-Gruppe. Keine Morbidität aufgrund von SAB oder aufgrund der damit verbundenen arteriellen Hypotension wurde festgestellt.

ANESTESIA GENERAL Y DE LA ESPINA PARA LA SUSTITUCION TOTAL DE LA CADERA: FRECUENCIA DE TROMBOSIS EN VENA PROFUNDA

SUMARIO

En 85 pacientes sometidos a sustitución total de la cadera se undujo bloqueo subaracnoideo o anestesia general La frecuencia de trombosis en vena profunda, evaluada mediante estudios de venografía y de absorción de fibrinogen, fue del 29% para aquellos pacientes bajo bloqueo subaracnoideo y del 54% para el grupo de anestesia general. La pérdida total de sangre (durante la operación y teniendo en cuenta el drenaje de la herida después de aquella) fue del 66% para el grupo con bloqueo subaracnoideo y el volumen total de transfusiones fue del 52%, en relación al grupo de anestesia general. No se detectó mortalidad atribuida al bloqueo subaracnoideo ni a la hipotensión arterial asociada

Br. J. Anaesth. (1980), **52**, 1123

MOTOR NERVE CONDUCTION IN INTRAVENOUS REGIONAL ANAESTHESIA WITH BUPIVACAINE HYDROCHLORIDE

F. MAGORA, L. STERN AND A. MAGORA

SUMMARY

Motor nerve conduction (MNC) from proximal and distal points of the median and ulnar nerves was examined in 14 patients receiving a total of 29 i.v. regional anaesthetics (IRA) with bupivacaine hydrochloride in doses ranging from 100 to 300 mg. Conduction was tested during and following vascular obstruction, until MNC returned to pre-IRA value. After 20 min of obstruction, MNC was unobtainable in most patients, an effect which was dose-related. The action of bupivacaine on MNC persisted for up to 3 h after cuff release, depending on the dose, and paralleled voluntary movements. MNC block began at the proximal point of both nerves, the median nerve being affected earlier. Based on the clinical and electrical findings, bupivacaine 200 mg proved to be the optimum dose for producing safe and prolonged IRA.

Local anaesthetic agents block nerve conduction, as demonstrated by a progressive decrease in amplitude of the evoked response, and a delay of response and slower velocity of conduction. The effect, which is reversible, is more marked in sensory than in motor fibres (Mazzarella, Bravaccio and Memoli, 1966; de Jong and Nace, 1968). I.v. regional anaesthesia (IRA) with lignocaine hydrochloride results in the same phenomena, but only for as long as the sphygmomanometer cuff remains inflated (Shanks and McLeod, 1970).

The analgesic effect of bupivacaine hydrochloride, on the other hand, may persist for a variable time after cuff release (Watson, Brown and Reich, 1970; Evans et al., 1974; Magora et al., 1978). This characteristic action of the drug has been attributed to its strong binding power to the nerve lipoproteins (Tucker and Boas, 1971).

Motor nerve conduction (MNC) studies were carried out during and after release of vascular obstruction, to assess the effects of IRA with bupivacaine. The results were compared with the values of MNC before IRA, and correlated with clinical evidence of analgesia and motor weakness.

PATIENTS AND METHODS

Fourteen patients were studied: seven suffered from shoulder–hand syndrome, three from causalgia, two from sympathetic reflex dystrophy, one from painful spasticity, and in one patient IRA was administered to evaluate release of elbow and wrist flexion contracture. The nature of the treatment and examination was explained to the patient and informed consent was obtained in all instances.

Three patients received IRA with 100 mg of bupivacaine (40 ml, 0.25%), five with 150 mg (60 ml, 0.25%), 14 with 200 mg (40 ml, 0.50%) and seven with 300 mg (60 ml, 0.50%). In nine patients, IRA was induced more than once.

Vascular obstruction was maintained for 20 min, after which the cuff was released in an on–off manner, repeated four or five times, each deflation lasting 10 s and each re-inflation continuing for 50 s. The patient was under constant medical observation throughout the procedure.

MNC was assessed for the ulnar and median nerves, the signals being picked up by coaxial needle electrodes placed in the abductor digiti minimi and opponens pollicis muscles, respectively. Supramaximal stimuli of 0.5 ms duration were given at the proximal (elbow) and distal (wrist) points of the nerves, both these points being located below the tourniquet. Amplitude, duration and delay of the evoked response were measured and recorded. MNC was examined before administration of IRA, at intervals of 5 min during the 20-min vascular obstruction, and every 5–15 min after cuff release until the measurements

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Presented at the Fifth European Congress of Anesthesiology, Paris, 1978.

0007-0912/80/111123-07 $01.00

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had returned to the values recorded before IRA. For purposes of comparison, four of the patients received lignocaine 40 ml (0.5% solution) also, while vascular obstruction was maintained for 40 min.

Concomitant with the MNC assessments, voluntary finger movements, analgesia (pin-prick) and touch sensation including the subjective feeling of numbness, were assessed. Whenever the clinical effects persisted for more than 1 h after the release of vascular obstruction, MNC was re-examined at 30-min intervals until the value had returned to normal.

RESULTS

Since the smallest degree of variability occurred in the delay of the evoked response while, at the same time, it reflected the changes encountered in the other indices, the tabulated results relate to the value of delay (latency) only.

The tables include the average latencies in the respective groups of patients before, at pre-set times during, and for various intervals after vascular obstruction. In parentheses are the numbers of patients in whom no response could be elicited (minus signs), or in whom the delay returned to the pre-IRA value (n-sign).

TABLE I *Delay of evoked response in the median and ulnar nerves under i.v. regional anaesthesia with bupivacaine hydrochloride 100 mg (40 ml, 0.25%) in three patients (average values).* *n = *number of patients in whom the delay returned to pre-IRA values*

		Median		Ulnar	
Vascular obstruction	Time (min)	Proximal (ms)	Distal (ms)	Proximal (ms)	Distal (ms)
Before		7.4	3.7	7.7	3.2
During	5	8.9	4.1	8.7	3.9
	10	9.3	4.3	9.4	4.1
	15	10.8	4.3	10.8	4.2
	20	11.3	4.4	11.9	4.4
After	5	9.2	4.1	9.1	4.0
	10	9.3	3.9	9.1	4.0
	20	7.8	3.6	7.9	3.0
	30	7.6	*$n = 3$	7.6	$n = 3$
	45	$n = 3$		$n = 3$	

TABLE II. *Delay of evoked response in the median and ulnar nerves under i.v. regional anaesthesia with bupivacaine hydrochloride 150 mg (60 ml, 0.25%) in five patients (average values).* †*Minus sign denotes the number of patients in whom the MNC had disappeared,* *n = *number of patients in whom delay had returned to pre-IRA values*

		Median		Ulnar	
Vascular obstruction	Time (min)	Proximal (ms)	Distal (ms)	Proximal (ms)	Distal (ms)
Before		7.5	3.7	7.8	3.0
During	5	9.9 (−1)†	3.8 (−1)	8.4 (−1)	3.3
	10	10.4 (−1)	4.2 (−1)	9.1 (−2)	4.1
	15	8.8 (−3)	4.8 (−1)	10.2 (−2)	4.2
	20	(−5)	5.6 (−3)	10.5 (−2)	5.1 (−1)
After	5	9.0 (−3)	5.3 (−1)	9.7 (−1) ($n = 1$)*	3.7 ($n = 2$)
	10	9.5 (−2)	4.7	9.5 (−1) ($n = 1$)	3.6 ($n = 2$)
	20	9.4 (−1)	4.6 ($n = 1$)	8.3 (−1) ($n = 1$)	3.2 ($n = 2$)
	30	9.5	4.5 ($n = 1$)	7.9 ($n = 2$)	3.2 ($n = 2$)
	45	9.3 ($n = 1$)	5.6 ($n = 3$)	7.9 ($n = 2$)	3.2 ($n = 3$)
	60	9.0 ($n = 2$)	($n = 5$)	($n = 5$)	3.2 ($n = 3$)
	120	($n = 5$)			($n = 5$)

IRA with bupivacaine 100 mg (*table I, fig. 1*). During vascular obstruction there was a prolonged delay of conduction in the median and ulnar nerves, from both the proximal and distal points of stimulation. The delay returned to pre-IRA values within 45 min of tourniquet release. The evoked response did not disappear in any of the three patients.

IRA with bupivacaine 150 mg (*table II; fig. 2*). An increase in delay was apparent within the first 5 min, being more pronounced at the proximal point of both nerves. At 20 min of obstruction, there was no evoked response from the proximal point of the median nerve in any of the five patients, while in three no response was elicited from the distal point. In the ulnar nerve, conduction was completely blocked proximally in two patients and distally in one. When a response could be obtained, the delay was markedly longer.

Upon release of vascular obstruction, the effects from the proximal point of the median nerve were more prolonged. Thirty minutes later, only a

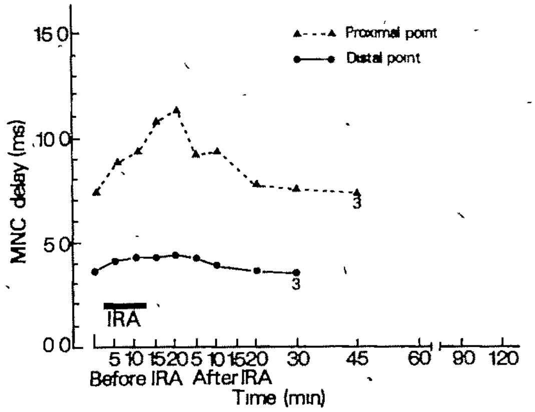

FIG. 1. Average delay of evoked response in the median nerve under i.v. regional anaesthesia with bupivacaine hydrochloride 100 mg (40 ml, 0.25%) in three patients. Minus sign (−) denotes the number of patients in whom MNC had disappeared. The numbers without a sign indicate number of patients in whom delay had returned to values recorded before IRA.

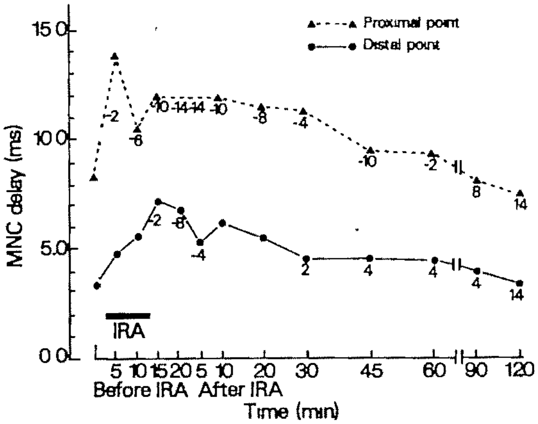

FIG. 3. Average delay of evoked response in the median nerve under i.v. regional anaesthesia with bupivacaine hydrochloride 200 mg (40 ml, 0.5%) in 14 patients. Minus sign (−) denotes the number of patients in whom the MNC had disappeared. The numbers without a sign indicate number of patients in whom delay had returned to values recorded before IRA.

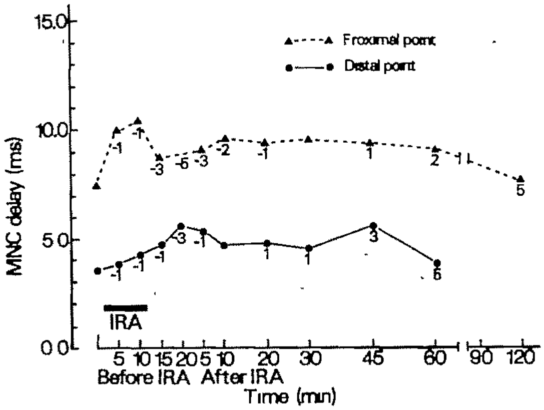

FIG. 2. Average delay of evoked response in the median nerve under i.v. regional anaesthesia with bupivacaine hydrochloride 150 mg (60 ml, 0.25%) in five patients. Minus sign (−) denotes the number of patients in whom the MNC had disappeared. The numbers without a sign indicate number of patients in whom delay had returned to values recorded before IRA.

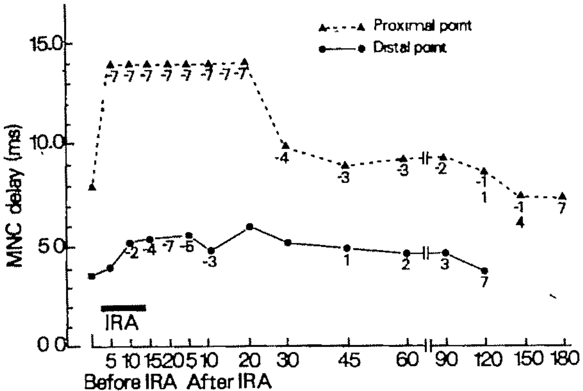

FIG. 4. Average delay of evoked response in the median nerve under i.v. regional anaesthesia with bupivacaine hydrochloride 300 mg (60 ml, 0.5%) in seven patients. Minus sign (−) denotes the number of patients in whom the MNC had disappeared. The numbers without a sign indicate number of patients in whom delay had returned to values recorded before IRA.

diminished response could be elicited in all the patients; at 2 h, all had returned to normal. Similar phenomena, but to a lesser degree, were noted from the distal point of the median nerve with a return to normal at 1 h after release of the tourniquet.

In the ulnar nerve, the effects were less marked: at 5 min following cuff release, the delay from the proximal point had returned to normal in one, and from the distal point in two patients; within 1 h all values had returned to normal.

TABLE III. *Delay of evoked response in the median and ulnar nerves under i.v. regional anaesthesia with bupivacaine hydrochloride 200 mg (40 ml, 0.5%) in 14 patients (average values). †Minus sign denotes the number of patients in whom the MNC had disappeared; *n = number of patients in whom delay had returned to pre-IRA values*

		Median		Ulnar	
Vascular obstruction	Time (min)	Proximal (ms)	Distal (ms)	Proximal (ms)	Distal (ms)
Before		8.3	3.4	7.5	3.0
During	5	14.0 (−2)†	4.9	9.1	3.5
	10	10.7 (−6)	5.7	9.3 (−4)	3.9
	15	12.0 (−10)	7.2 (−2)	10.2 (−4)	4.4
	20	(−14)	6.9 (−8)	10.9 (−6)	4.3 (−2)
After	5	(−14)	5.3 (−4)	9.4 (−6)	4.0 (−2)
	10	12.0 (−10)	6.2	8.9 (−4)	4.0
	20	11.5 (−8)	5.6	8.1 (−4) ($n = 2$)*	3.9 ($n = 2$)
	30	11.3 (−4)	4.7 ($n = 2$)	7.9 (−4) ($n = 4$)	3.8 ($n = 4$)
	45	9.6 (−4)	4.7 ($n = 4$)	8.4 (−2) ($n = 6$)	3.7 ($n = 12$)
	60	9.4 (−2) ($n = 4$)	4.6 ($n = 4$)	8.2 ($n = 8$)	($n = 14$)
	90	9.1 ($n = 8$)	4.0 ($n = 4$)	8.3 ($n = 8$)	
	120	($n = 14$)	($n = 14$)	($n = 14$)	

TABLE IV. *Delay of evoked response in the median and ulnar nerves under i.v. regional anaesthesia with bupivacaine hydrochloride 300 mg (60 ml, 0.5%) in seven patients (average values). †Minus sign denotes the number of patients in whom the MNC had disappeared; *n = number of patients in whom delay had returned to pre-IRA values*

		Median		Ulnar	
Vascular obstruction	Time (min)	Proximal (ms)	Distal (ms)	Proximal (ms)	Distal (ms)
Before		8.0	3.7	8.1	3.1
During	5	(−7)†	4.0 (−1)	10.8 (−2)	4.3 (−1)
	10	(−7)	5.2 (−2)	12.8 (−4)	4.3 (−2)
	15	(−7)	5.4 (−4)	(−7)	5.0 (−5)
	20	(−7)	(−7)	(−7)	6.0 (−6)
After	5	(−7)	5.6 (−5)	(−7)	6.3 (−5)
	10	(−7)	4.8 (−3)	13.2 (−5)	5.2 (−4)
	20	14.0 (−5)	6.0	12.8 (−4)	5.0 (−4)
	30	10.0 (−4)	5.2	12.0 (−4)	4.0 (−3)
	45	9.0 (−3)	4.8 ($n = 1$)*	10.2 (−4)	3.6 (−1) ($n = 1$)
	60	9.2 (−3)	4.7 ($n = 2$)	9.8 (−3)	4.0 ($n = 2$)
	90	9.3 (−2)	4.6 ($n = 3$)	9.5 (−1)	3.8 ($n = 3$)
	120	8.6 (−1) ($n = 1$)	($n = 7$)	8.9 (−1) ($n = 1$)	3.5 ($n = 5$)
	150	8.4 (−1) ($n = 4$)		8.8 (−1) ($n = 2$)	($n = 7$)
	180	($n = 7$)		8.7 (−1) ($n = 3$)	
	240			9.6 (−1) ($n = 4$)	
	270			($n = 7$)	

IRA with bupivacaine 200 mg (table III, fig. 3). The results were similar to those obtained for IRA with bupivacaine 150 mg; again, the effects were more marked in the median nerve and from the proximal points of both nerves. The delay values returned to normal within 1–2 h of cuff release.

IRA with bupivacaine 300 mg (table IV, fig. 4). In all seven patients, the evoked response became unobtainable from the proximal point of the median nerve within 5 min of vascular obstruction, and from the ulnar nerve within 15 min. From the distal point of the median nerve no response occurred after 20 min of obstruction in any of the patients; in six subjects, the response (from the distal point) from the ulnar nerve was absent. In all patients, and from both nerves, this quantity of bupivacaine (300 mg) resulted in effects that were more prolonged than at smaller doses. The delay in nerve conduction from the distal point returned to normal 2 h after cuff release (slightly longer in the ulnar nerve), and from the proximal point of stimulation it reverted to normal within 3 h in the median and 4.5 h in the ulnar nerve.

In the four patients who received IRA with lignocaine 200 mg, the effects upon MNC were similar to those of bupivacaine but of a much shorter duration. The delay returned to pre-IRA values within 20–30 min following release of the vascular obstruction.

On clinical assessment, the muscle strength followed the findings with MNC: movement reappeared after nerve conduction had become obtainable again; prolonged delay in conduction was accompanied by severe muscle weakness, and muscle power returned to normal within 1 h after MNC had returned to pre-IRA values. Partial sensory loss persisted in all patients for longer periods of time, and there was a subjective feeling of numbness for up to 14 h.

Except for transient drowsiness in two patients, there were no signs of toxicity (such as uncontrolled movement, arrhythmia, significant changes in arterial pressure) in any instance.

DISCUSSION

The clinical and electrical effects of i.v. regional anaesthesia with bupivacaine may continue for various periods of time after release of vascular obstruction. These effects are characterized by persistent numbness, analgesia, weakness and partial or complete block of motor nerve conduction. The block is demonstrated by the disappearance or prolonged latency and low amplitude of the evoked response (de Jong and Nace, 1968; Shanks and McLeod, 1970).

IRA with lignocaine resulted in blockage of conduction during vascular obstruction, which started to return to normal within 5 min of cuff release and reached pre-IRA values within 20 min. Under bupivacaine anaesthesia, the nerve conduction block persisted for up to 3 h, with a slow and general return to normal. Lignocaine effects on nerve conduction similar to those of bupivacaine were reported by Shanks and McLeod (1970). Furthermore, the influence of bupivacaine cannot be attributed to the limb ischaemia *per se*, mainly because the period of vascular obstruction during IRA with lignocaine was 40 min as compared with 20 min when using the former drug. Shanks and McLeod (1970) and Hainaut and Goldé (1976) have demonstrated that the electrical changes in nerve conduction caused by 20-min limb ischaemia disappear within a few minutes of tourniquet release. The observations on bupivacaine and MNC are strengthened by the fact that IRA with both bupivacaine and lignocaine was carried out on the same patients.

Bupivacaine began to exert its activity within 5 min of cuff inflation, irrespective of dose; the effect became maximal at 15–20 min, and persisted after release of obstruction. Because the maximum effects seem to occur at 20 min, and analgesia persists after cuff release, the cuff may be deflated after this period of time if it is thought desirable for other reasons.

The block of nerve conduction caused by IRA with bupivacaine was dose-related both during and after vascular obstruction. The lowest intensity of effect was noted using 100 mg, while maximum blockage of MNC occurred with doses of 300 mg of bupivacaine.

Comparison of conduction in the two nerves examined shows that the effects were more pronounced in the median nerve with small doses of bupivacaine, while at greater doses, the block and delay of conduction were similar in both nerves. The earlier effect upon the median nerve may be explained by the larger venous channels surrounding the nerves in the anteromedial compartment of the elbow (Raj et al., 1972).

The block of conduction in both nerves appeared first at the proximal point (elbow) and spread centrifugally and the intensity of the effect was also more pronounced at this point. This indicates that the block originates in the nerve trunk, as already demonstrated in IRA with lignocaine (Sorbie and Chacha, 1965; Fleming et al., 1966; Shanks and McLeod, 1970). Although neither the myoneural junction nor the terminal fibres of the nerves were examined, it may be that they were affected to some extent also. The return to normal nerve conduction started distally (wrist).

Restoration of normal clinical and electrical function commenced 5–15 min following cuff release, but analgesia, weakness and abnormal MNC persisted for at least 20 min with injection of bupivacaine 100 mg and up to 240 min with 200 and 300 mg of the drug. In general, the muscle weakness paralleled MNC values, while sensory loss slightly preceded the slowing of conduction and continued in a patchy form for 1–3 h after MNC had returned to normal. A subjective feeling of numbness and clumsiness was present in 19 of the 29 IRA administered which continued for 6–20 h subsequent to cuff release in spite of a normal MNC. This manifestation was more pronounced with the greater doses of bupivacaine. Analgesia and weakness were present during IRA, even when an evoked response was still obtainable. In these instances, however, the evoked response was prolonged and the amplitude remained less than 1 mV. This discrepancy between MNC and clinical analgesia is explained by the fact that nerve conduction demonstrates the state of nerve fibres with large diameters, while painful stimuli are transmitted by fibres with small diameter. This mode of action was proved by Rosenfalck (1969), who showed that a slowing of conduction to half the normal value was not accompanied by an impairment of touch sensation, by Collins, Nulsen and Clark (1960) who demonstrated that painful stimulation was not perceived although conduction of alpha, beta and gamma fibres remained normal, and by Wencker, Nolte and Fruhstorfer (1975) who found normal electrical activity before the muscle power had recovered completely.

MNC has proved to be a reliable indicator of the duration of the effects of IRA upon voluntary movements. Although marked individual variations in intensity and extent of both clinical and electrical effects were noted, it was demonstrated objectively that bupivacaine had a prolonged effect after cuff release in all patients (Magora et al., 1980).

As the clinical effects, especially sensory, were similar with doses of bupivacaine 200 mg and 300 mg and the MNC was similar at doses of bupivacaine 150 mg and 200 mg, it is recommended that for analgesic–therapeutic purposes IRA be carried out with bupivacaine 200 mg. This quantity permits continuation of surgery or intensive physiotherapy under conditions of analgesia after the release of the tourniquet.

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CONDUCTION DU NERF MOTEUR DANS UNE ANESTHESIE REGIONALE ADMINISTREE PAR VOIE INTRAVEINEUSE A L'AIDE DE CHLORHYDRATE DE BUPIVACAINE

RESUME

On a procédé à des études sur la conduction du nerf moteur (MNC) à partir de points proximaux et distaux des nerfs médian et ulnaire sur 14 patients recevant au total 29 injections intraveineuses d'agents anesthésiants régionaux (IRA), contenant du chlorhydrate de bupivacaine en doses allant de 100 mg à 300 mg. La conduction a été soumise à des essais pendant et après une obstruction vasculaire, jusqu'à ce que la MNC revienne à sa valeur d'avant l'IRA. Après 20 min d'obstruction, il était virtuellement impossible de percevoir la MNC de la plupart des patients, effet qui était lié à la dose. L'action de la bupivacaine sur la MNC a persisté pendant près de trois heures après le retrait du manchon, ceci étant fonction de la dose et de mouvements volontaires effectués en parallèle. Le blocage de la MNC a commencé au point proximal des deux nerfs, le nerf médian étant affecté le premier. Sur la base des constatations cliniques et électriques, la bupivacaine administrée à raison de doses de 200 mg semble avoir été la dose optimale capable de produire en toute sécurité l'IRA prolongée.

MOTORNERVENLEITUNG BEI INTRAVENÖSER LOKALANÄSTHESIE MIT BUPIVACAIN-HYDROCHLORID

ZUSAMMENFASSUNG

Motornervenleitung (MNC) von proximalen und distalen Punkten des Median und des Ulnarnervs wurden bei 14 Patienten unter intravenöser Lokalanasthesie (IRA) untersucht—bei insgesamt 29 Spritzen von Bupivacain-Hydrochlorid in Dosen von 100–300 mg. Die Nervenleitung wurde wahrend und nach Gefässhemmung getestet, bis MNC zum Vor-IRA-Wert zuruckkehrte. Nach 20minutiger Hemmung war MNC bei den meisten Patienten nicht mehr vorhanden—eine dosisbezogene Wirkung. Die Bupivacain-Wirkung auf MNC Hielt bis zu 3 Stunden nach Knebeloffnung an, je nach Dosis, parallel zu beabsichtigten Bewegungen. Die MNC-Blockierung begann am Proximalen Ende beider Nerven, wobei der Mediannerv eher beeinflusst wurde. Aufgrund klinischer und elektrischer Resultate ergaben sich 200 mg Bupivacain als optimale Dosis zur Erzielung einer sicheren und verlängerten IRA

CONDUCCION DEL NERVIO MOTOR EN LA ANESTESIA INTRAVENOSA LOCAL USANDO HIDROCLORURO DE BUPIVACAINA

SUMARIO

Se examinó la conducción del nervio motor desde puntos próximos y distantes de los nervios mediano y cubital en 14 pacientes que recibieron un total de 29 anestésicos intravenosos locales usando hidrocloruro de bupivacaina en dosis que oscilaron entre 100 y 300 mg. La conducción se observó durante la obstrucción vascular, y después de ésta, hasta que aquella volvió a su valor previo a la administración de los anestésicos. La conducción del nervio motor no se consiguió después de una espera de 20 min en la mayoría de los pacientes, efecto que vá en función de la dosis. La influencia de la bupivacaina persistió en la conducción del nervio motor hasta un máximo de 3 h después de soltar el yugo, en función de la dosis, y de los movimientos voluntarios en paralelo El bloqueo de la conducción del nervio motor comenzó en los puntos próximos de ambos nervios, siendo afectado antes el nervio mediano. En base a los resultados clínicos y eléctricos, 200 mg de bupivacaina demostraron ser la dosis óptima para producir seguros y prolongados anestésicos intravenosos locales.

Br. J. Anaesth. (1980), 52, 1131

PROLONGED EFFECT OF BUPIVACAINE HYDROCHLORIDE AFTER CUFF RELEASE IN I.V. REGIONAL ANAESTHESIA

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SUMMARY

Bupivacaine hydrochloride 0.25% and 0.50% solutions, were administered 115 times by the i.v. regional route to 64 surgical patients and in 38 subjects suffering from pain syndromes. The clinical effects were limb numbness up to 20 h following cuff release, while analgesia and weakness of the limb muscles were evident 5 h after the tourniquet. Clinical and electrophysiological findings revealed a dose relationship of the effects. Toxic signs were noted in three patients in whom the cuff was released in a one-step fashion. In 11 patients, mean arterial plasma concentrations of bupivacaine reached 3.7 $\mu g\ ml^{-1}$ after administration of 0.5% bupivacaine 40 ml, 5 min after final cuff release, and decreased gradually thereafter. In selected conditions which do not require a bloodless field and in certain intractable pain states, i.v. regional anaesthesia with high-dose bupivacaine (200 mg of 0.5% solution) may be a simple and effective technique.

I.v. regional anaesthesia (IRA) with small concentrations of local anaesthetic agents is an accepted simple and safe technique of analgesia. However, with most drugs the effect wanes within 3–10 min of release of the blood vessel obstruction (Dunbar and Mazze, 1967; Brown, 1969; Shanks and McLeod, 1970). The main use of IRA has been in brief surgical procedures of the limb, carried out during cuff inflation. Some operations, such as in plastic surgery, do not require a bloodless field and they may last for more than an hour. In such instances, this form of anaesthesia becomes inadequate, mainly because of the necessity to deflate the tourniquet, which results in loss of analgesia. Certain pain syndromes of the upper limb require prolonged periods of physical mobilization, which is impossible without the aid of adequate local analgesia (Omer and Thomas, 1971). One such condition is sympathetic reflex dystrophy in its various forms and, especially, the shoulder–hand syndrome which follows a stroke and which is often accompanied by spasticity. Stellate ganglion block or peripheral nerve block are not always efficient and may be of insufficient duration for physical mobilization. For these reasons, a technique of regional analgesia which does not require prolonged vascular obstruction and which is applied with a long-acting anaesthetic agent was sought. Bupivacaine hydrochloride is such an agent; the administration of 40 ml of a 0.25% solution results in an effect similar to that obtained with other diluted solutions of local anaesthetic agents (Ware, 1975, 1976). On the other hand, Watson, Brown and Reich (1970) and Evans and others (1974) have reported that 0.25% bupivacaine has a residual analgesic effect that extends beyond the release of vascular obstruction.

In previous clinical trials, we found that 0.25% bupivacaine 50 ml does not produce adequate analgesia for either prolonged limb surgery without tourniquet or the physical therapy of pain syndromes with or without spasticity.

In the present study we assessed the effects of IRA using bupivacaine solutions of 0.25% and 0.50% and in various quantities in an attempt to determine the optimal dosage for prolonged and safe regional anaesthesia.

PATIENTS AND METHODS

One hundred and fifteen IRA's were administered to 102 patients, ranging in age from 19 to 65 yr (table I). Most patients received premedication with oral diazepam 5–10 mg 1 h before surgery and, if necessary during prolonged procedures, diazepam was administered i.v. for sedation. No

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Presented at the Fifth European Congress of Anesthesiology, Paris, 1978.

0007-0912/80/111131-06 $01.00

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medication was given to any of the patients who received IRA as a treatment for pain.

TABLE I. *Type and duration of surgical procedures and diagnosis of pain syndromes*

Surgical procedure	No. of patients	Duration (min)
Bone surgery	12	90–150
Decompression of peripheral nerve	15	30–90
Reimplantation of fingers	4	180–240
Arteriovenous shunt	11	60–120
Soft tissue surgery	13	45–90
Tenotomy	9	30–60

Pain conditions	No of patients	No. of IRA
Causalgia major	7	9
Sympathetic reflex dystrophy	10	14
Shoulder–hand syndrome	21	28

Following exsanguination of the limb, bupivacaine was injected into a distal vein of the hand. The vascular obstruction was maintained for 20 min, and the occluding cuff was released by deflation and inflation five times, each deflation lasting 10 s and each inflation 50 s. The doses of bupivacaine used are in table II.

The local effects of bupivacaine were evaluated continuously during the vascular obstruction and for a period of up to 20 h after IRA administration. Arterial pressure, e.c.g. and heart rate were continuously monitored throughout IRA, with special attention being paid to any sign of clinical toxicity.

Gas chromatographic determination of the bupivacaine concentrations in arterial plasma was performed in 13 patients (Zylber-Katz, Granit and Levy, 1978), who received bupivacaine 200 mg (3–4 mg/kg body weight).

Motor nerve conduction studies of the ulnar and median nerves from the proximal and distal points were carried out 29 times in 14 patients who had received various doses of bupivacaine (Magora, Stern and Magora, 1980).

RESULTS

Complete anaesthesia and motor weakness occurred in all patients during obstruction of the circulation and persisted for various periods of time after cuff release. These effects ensured appropriate conditions for prolonged surgery and for painless physiotherapy (table III).

TABLE III. *Duration of clinical effects of i.v. regional anaesthesia (IRA) with bupivacaine hydrochloride after release of tourniquet*

Dose of bupivacaine	Duration of anaesthesia	
	Analgesia	Weakness
60 ml (0.25%)	Up to 30 min	10–30 min
40 ml (0.50%)	1–4 h	2–4 h
60 ml (0.50%)	2–5 h	4–5 h

Numbness of the treated limb was felt for up to 20 h after IRA. Anaesthesia appeared initially in the proximal area of the limb and spread distally. The return of normal sensation started in the hand and continued slowly towards the forearm. Motor weakness followed the same pattern.

The surgical procedures lasted for periods ranging from 30 min to 4 h following cuff release. When necessary for the operation, the tourniquet was re-applied, but no additional administration of bupivacaine was required when the cuff was released again. Except for transient drowsiness in three patients, no other signs of toxicity such as arrhythmia, significant changes in arterial pressure, involuntary movements, slurring of the

TABLE II. *Volume and concentration of bupivacaine hydrochloride during i.v. regional anaesthesia (IRA)*

Dose of bupivacaine		Number of IRA		
Volume	Concentration	Surgery of upper limb	Surgery of lower limb	Pain and/or spastic contractures of upper limb
60 ml	0.25% (150 mg)	—	—	6
40 ml	0.50% (200 mg)	60	—	36
60 ml	0.50% (300 mg)	—	4	9

TABLE IV. *Arterial plasma bupivacaine hydrochloride (BH) concentrations following i.v regional anaesthesia (IRA)*

				Plasma concentrations of BH (μg ml⁻¹)					
				During intermittent release of tourniquet (min)		After final release of tourniquet (min)			
Patient No.	Sex	Age (yr)	Wt (kg)	1–2	3–4	5	10	20	30
1	F	48	65	0.5	0.9	2.2	3.8	3.2	2.1
2	F	36	63	1.3	0.8	1.9	2.7	1.3	1.6
3	M	39	54	0.5	0.5	3.8	2.0	1.4	1.1
4	M	64	80	0	0.4	4.1	2.5	1.5	1.4
5	F	75	60	0	0.9	5.2	6.4	4.1	4.0
6	F	80	54	0	6.1	3.7	3.0	2.4	1.5
7	F	70	50	0	0	3.9	2.3	1.9	1.9
8	F	49	62	1.2	2.6	3.9	2.9	1.1	1.8
9	M	40	83	1.0	4.3	4.8	2.6	2.0	1.3
10	M	73	75	4.4	2.4	4.2	1.9	1.2	1.2
11	M	70	65	0.5	1.7	3.2	2.9	2.4	2.1
Mean		58.5	64.6	0.9	1.9	3.7	3.0	2.0	1.8
±SEM		4.9	3.2	0.4	0.6	0.3	0.4	0.3	0.2

speech, numbness of the tongue or lightheadedness occurred.

In 11 of the patients, in whom the tourniquet was released by intermittent deflation and inflation during 4–5 min, the mean bupivacaine plasma concentrations during this period ranged from 0.9 μg ml⁻¹ to 1.9 μg ml⁻¹. At 5 min after final cuff release, bupivacaine values reached a mean concentration of 3.7 μg ml⁻¹ and thereafter decreased gradually to a mean of 1.8 μg ml⁻¹ at 30 min (table IV, fig. 1).

In three subjects who received bupivacaine 200 mg, the cuff was inadvertently released in a sudden manner after 20 min of occlusion. Ten minutes later, toxic reactions occurred in all three—generalized convulsion in one patient and unusual behaviour in another. The arterial plasma concentrations of bupivacaine in these two patients immediately after cuff release were 7.1 μg ml⁻¹ and 8.3 μg ml⁻¹, respectively, decreasing to 3.2 μg ml⁻¹ and 4.1 μg ml⁻¹ after 5 min. In the third patient, a curare-like reaction was observed, with ptosis and partial loss of muscle power, both effects persisting for 30 min.

During and after vascular obstruction, motor nerve conduction showed a prolonged latency and low amplitude of evoked potentials for differing periods of time in all patients and at all dosages of bupivacaine administered (Magora, Stern and Magora, 1978).

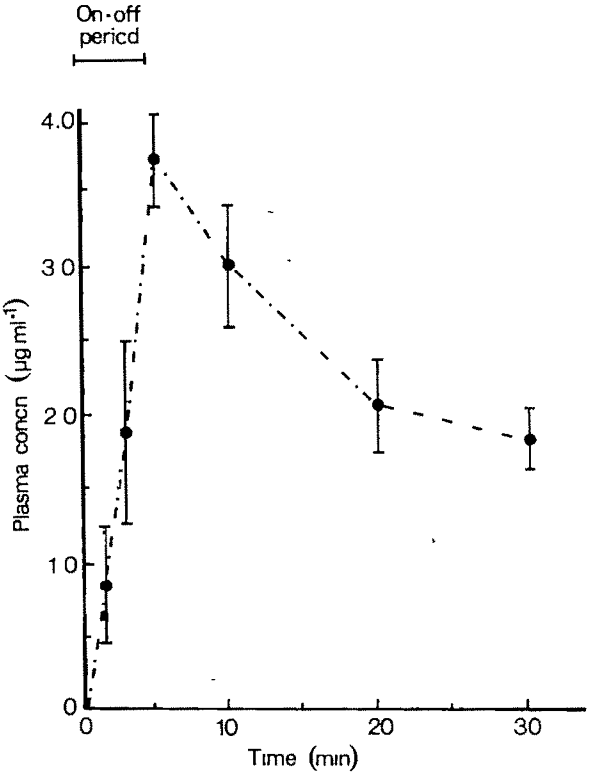

FIG. 1. Arterial plasma bupivacaine hydrochloride concentrations following i.v. regional anaesthesia (mean ± SEM; $n = 11$).

DISCUSSION

The duration of limb analgesia with bupivacaine was dose related: bupivacaine 150 mg did not cause prolonged analgesia in any of the subjects. Thus, a dose of 200 mg was tried with satisfactory effect. Despite clinically adequate analgesia, motor nerve conduction did not always disappear and it was decided to test the administration of bupivacaine 300 mg. This resulted in only slightly more pronounced clinical and electrical effects, which made its further use unnecessary and it was discontinued. The doses of bupivacaine 150 and 200 mg used in this study were greater than those normally required for IRA during surgery. However, a greater dose of bupivacaine may be warranted in some types of limb surgery or pain state for the purpose of obtaining prolonged analgesia after IRA. In 1977 Moore and others reported the administration of bupivacaine for extradural and nerve blocks, in quantities greater than 150 mg. Thus, for example, they gave in intercostal nerve blocks a dose of up to 600 mg of 0.75% bupivacaine, without observing any toxic effect. Based on these results, the group recommended that the accepted dosage of 2 mg per kg body weight be reassessed. However, it should be noted that their patients received i.v. barbiturates during and following the injection of bupivacaine, which may have prevented the manifestation of some toxic reactions.

In 11 patients the mean plasma concentration of bupivacaine reached 3.7 $\mu g\ ml^{-1}$ at 5 min after the final cuff release; this concentration was not associated with any sign of toxicity. Similar plasma concentrations (up to 4.0 $\mu g\ ml^{-1}$) were found after extradural, brachial plexus or peripheral nerve blocks, without convulsions (Moore et al., 1976). Toxic reactions may occur at plasma concentrations greater than 4.0 $\mu g\ ml^{-1}$, as in two of our patients and two others from the literature in whom bupivacaine entered the bloodstream inadvertently after extradural anaesthesia (Moore, Balfour and Fitzgibbons, 1979). Evidently, the pharmacokinetics of bupivacaine in IRA are not comparable with those in either extradural block or peripheral nerve blocks. With the IRA technique, peak plasma concentrations of the drug occur within a few minutes after release of the tourniquet. Thereafter they decrease rapidly, as was shown by Eriksson (1969), Tucker and Boas (1971), Ware (1976) and by the results of the present study. In certain instances greater concentrations may be missed in spot samples because of swift changes of bupivacaine concentrations in arterial blood.

On the other hand, if the effects of bupivacaine in IRA are compared with those obtained by direct i.v. injection of the drug, it seems that the rapidity of application (the "bolus" effect), and the subsequent blood concentrations, are the determining factors in toxicity. Mather, Long and Thomas (1971) demonstrated that arterial plasma concentrations of the drug greater than 10 $\mu g\ ml^{-1}$, if the injection was slow, were not followed by toxic reactions. It is therefore essential to release the tourniquet gradually, since periodic deflation and inflation of the cuff significantly reduce drug escape from the limb, as reported by Tucker and Boas (1971) and corroborated by the present investigation. Further support for the technique of intermittent cuff release comes from the three patients who manifested toxic reactions after the abrupt opening of the tourniquet, while in all our other subjects (including those who received bupivacaine 300 mg) but in whom the release of tourniquet was carried out in the "deflation–inflation" manner, no sign of toxicity appeared. Inadvertent release of the local anaesthetic agent to the bloodstream during IRA is always likely to cause signs of toxicity. As this danger is even more important when large doses of bupivacaine are used, such a leak in the blood should never be allowed. The equipment must be thoroughly checked before IRA and the recommended technique should be followed strictly.

It is reasonable to assume that the severe metabolic acidosis developing in the ischaemic limb under IRA (Déry et al., 1965) may also influence the distribution between the cells and the extracellular fluid of a weak base like bupivacaine (pKa = 8.1), thus reducing the quantity of drug entering the nerve. Injection of sodium bicarbonate will lessen limb acidosis and change the kinetics of bupivacaine release, thereby diminishing toxicity. The liberation of bupivacaine from the tissues would be slowed down, with resulting prolonged residual anaesthesia. This course of events is currently being investigated by us in man.

From the present clinical trials, it was evident that IRA with bupivacaine 150 mg (60 ml, 0.25%) results in only a brief period of analgesia and motor weakness after cuff release (table IV). IRA with bupivacaine 200 mg (40 ml, 0.5%) caused prolonged analgesia and motor weakness, lasting up to 4 h, followed by a feeling of numbness which persisted for up to 20 h. Similar effects of IRA were obtained with bupivacaine 300 mg (60 ml, 0.5%). As the clinical and electrical differences between administration of bupivacaine 200 mg and 300 mg were insignificant (table III) and as the toxicity of the latter dose is presumably greater, it was concluded that the optimal quantity of bupivacaine for prolonged analgesia after IRA is 200 mg for adults of average weight.

The clinical indications for the use of IRA with bupivacaine are limited to the following conditions:

(1) Prolonged limb surgery not requiring a bloodless field and where long-term analgesia after operation is desired to avoid undue vasospasm (for example, plastic surgery).

(2) Sympathetic reflex dystrophy in which prolonged and repeated periods of analgesia are necessary for the performance of intensive physiotherapy.

(3) Limb spasticity for trial of release of spastic contractures and eventual unmasking of existing movements.

Toxic systemic manifestations of bupivacaine can be avoided by rigorous observation of the gradual on–off cuff release, as was demonstrated by the lack of toxic effects and low blood concentration bupivacaine analysis, even after administration of bupivacaine 300 mg. The occurrence of toxicity in three of our patients can be ascribed to the sudden release of the cuff, an event that took place in the beginning of the trial, when we were not sufficiently aware of the importance of intermittent cuff release. As in any other toxic manifestation of local anaesthetic agents entering the circulation, diazepam i.v. is an excellent treatment. Obviously, the usual resuscitative equipment should be easily available.

ACKNOWLEDGEMENTS

This work was supported in part by a grant from the Joint Research Fund of the Hebrew University and Hadassah, and by the Salomon Katzenelenbogen Medical Research Fund.

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PROLONGATION DE L'EFFET DU CHLORHYDRATE DE BUPIVACAINE APRES RELACHEMENT DU MANCHON LORS D'UNE ANESTHESIE ADMINISTREE PAR VOIE INTRAVEINEUSE REGIONALE

RESUME

On a administré 115 fois des solutions de chlorhydrate de bupivacaïne à 0,25% et à 0,50% par la voie intraveineuse régionale, à 64 patients devant subir une intervention chirurgicale ainsi qu'à 38 sujets souffrant de syndromes de la douleur Les effets cliniques se sont manifestés par un engourdissement du membre, et dans certains cas pendant près de 20 h, après le relâchement du manchon, alors que l'analgésie et la faiblesse des muscles du membre sont restées évidentes jusqu'à 5 h après

le tourniquet Les constatations cliniques et électrophysiologiques ont révélé que les effets étaient fonction de la dose administrée. On a remarqué des effets toxiques sur trois patients sur lesquels le manchon avait été relâché d'un seul coup. Sur 11 patients, les concentrations artérielles moyennes de bupivacaïne dans le plasma ont atteint $3{,}7\ \mu g\ ml^{-1}$ après l'administration de 40 ml de bupivacaïne à 0,50%, 5 mn après le relâchement final du manchon, puis elles ont graduellement diminué. Dans des conditions spécialement choisies ne nécessitant pas un champ opératoire exsangue et dans certains autres états de douleurs rebelles, l'anesthésie administrée par voie intraveineuse régionale à l'aide d'une forte dose de bupivacaïne (200 mg d'une solution à 0,50%) semble être une technique simple et efficace.

VERLÄNGERTE WIRKUNG VON BUPIVACAIN-HYDROCHLORID NACH MANSCHETTENLÖSUNG BEI INTRAVENÖSER LOKALANÄSTHESIE

ZUSAMMENFASSUNG

Bupivacain-Hydrochlorid in Lösungen zu 0,25 und 0,50% wurde 115 mal intravenös an 64 Chirurgiepatienten und an 38 unter Schmerzsyndromen leidende Patienten verbreicht. Klinische Wirkungen waren gefuhllose Gliedmassen bis zu 20 Stunden nach Manschettenlösung, wahrend Schmerzlinderung und Schwäche der Gleidmassenmuskeln 5 Stunden nach Manschettenlösung evident waren. Klinische und elektrophysiologische Resultate zeigen eine Dosisbeziehung dieser Wirkungen. Toxische Anzeichen ergaben sich bei 3 Patienten, bei denen die Manschette aufeinmal gelost wurde. Bei 11 Patienten erreichten die mittleren Plasmakonzentrationen von Bupivacain $3{,}7\ \mu g\ ml^{-1}$ nach Verabreichung von 0,5% Bupivacain 40 ml und 5 Minuten nach endgultiger Manschettenlosung; dann sanken die Konzentrationen langsam ab. Bei bestimmten Bedingungen, die kein unblutiges Operationsfeld erfordern, sowie bei gewissen unbehandelbaren Schmerzzuständen könnte sich eine intravenose Lokalanasthesie mit hohen Dosen Bupivacain (200 mg einer 0,5%igen Losung) als einfache und wirksame Methode erweisen.

EFECTO PROLONGADO DEL HIDROCLORURO DE BUPIVACAINA EN LA ANESTESIA INTREVENOSA LOCAL DESPUES DE LIBERAR EL YUGO

SUMARIO

Se inyectaron soluciones al 0,25% y al 0,50% de hidrocloruro de bupivacaína, 115 veces y a través de la ruta intravenosa local, a 64 pacientes quirúrgicos y a 38 sujetos aquejando de síndromes de dolor. Los efectos clinicos después de liberar el yugo se presentaron en forma de entumecimiento de los miembros, al tiempo que cinco horas después del torniquete se apreció analgesia y debilidad de los músculos de los miembros. Los resultados clinicos y electrofisiológicos revelaron que los efectos van en función de la dosis. En tres de los pacientes se apreciaron efectos tóxicos, habiéndose liberado el yugo en una sóla etapa. En 11 de los pacientes la concentracion media de bupivacaína en el plasma arterial fue de $3{,}7\ \mu g\ ml^{-1}$ después de la administración de bupivacaína (40 ml) al 0,5%, cinco minutos después de liberar el yugo, disminuyendo gradualmente a continuación. En condiciones seleccionadas que no requieran un campo sin sangre y en ciertos casos de dolor intratable, la anestesia intravenosa local mediante una alta dosis de bupivacaína (solución de 200 mg al 0,5%) puede que sea una técnica simple y efectiva.

Br. J. Anaesth. (1980), 52, 1137

CARDIAC EFFECTS OF ATROPINE AND GALLAMINE IN PATIENTS RECEIVING SUXAMETHONIUM

J. VIBY-MOGENSEN, K. WISBORG AND O. SØRENSEN

SUMMARY

Eighty healthy patients were randomly allocated to four groups Atropine 0.01 mg kg^{-1} i.v (group I), gallamine 0.3 mg kg^{-1} i.v. (group II), atropine 0.01 mg kg^{-1} i.m. and gallamine 0.3 mg kg^{-1} i.v (group III), or atropine 0.01 mg kg^{-1} i.v. and gallamine 0.3 mg kg^{-1} i.v. (group IV) were given before operation. After induction of anaesthesia with thiopentone, suxamethonium 1 mg kg^{-1} was given i.v The lungs were ventilated with halothane in nitrous oxide in oxygen. Five minutes later the same dose of suxamethonium was repeated. E.c.g. was monitored continuously. No serious bradycardia was observed following a second injection of suxamethonium in any group. The results suggest that thiopentone protects against suxamethonium-induced bradycardia during halothane anaesthesia.

Severe arrhythmia and asystole are well-known complications of repeated doses of suxamethonium (Martin, 1958; Bullough, 1959; Lupprian and Churchill-Davidson, 1960; Mathias and Evans-Prosser, 1968). In previous studies, we have examined the protective effect of atropine and gallamine when given before halothane (Viby-Mogensen et al., 1976; Wisborg, Christensen and Viby-Mogensen, 1977). Only atropine in doses causing considerable tachycardia protected against bradycardia and gallamine did not give sufficient protection even in doses causing severe tachycardia and a high frequency of unpleasant side-effects. These results seem inconsistent with those reports in which atropine and small doses of non-depolarizing neuromuscular blockers have been found to protect against severe arrhythmia following repeated doses of suxamethonium (Verner and Comty, 1959; Lupprian and Churchill-Davidson, 1960; Mathias, Evans-Prosser and Churchill-Davidson, 1970; Karhunen, Heinonen and Tammisto, 1972; Stoelting, 1977). However, our studies were conducted in patients who did not receive a barbiturate, whereas the patients in the other studies did, and did not receive halothane. Williams and others (1961) and Shoenstadt and Whitcher (1963) found that thiopentone protected against severe changes in cardiac rhythm following suxamethonium.

We have studied the effect of a second dose of suxamethonium after preoperative administration of atropine, gallamine or an i.v. combination in patients in whom anaesthesia was induced with thiopentone and maintained with halothane.

PATIENTS AND METHODS

Patients

Eighty healthy patients who underwent minor surgical procedures and gave consent to the study were allocated randomly to four groups.

Premedication was given i.m. 1h before induction of anaesthesia and the drugs under study were given i.v. 3 min before injection of thiopentone (table I).

Anaesthesia (fig. 1)

Three minutes before induction atropine or gallamine or both was administered i.v. according to group. Anaesthesia was induced by slow injection of thiopentone 4–5 mg kg^{-1} i.v. until the

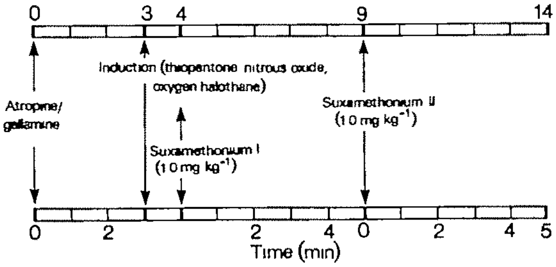
0
3
4
9
14
Induction (thiopentone nitrous oxide, oxygen halothane)
Atropine/ gallamine
Suxamethonium I (1.0 mg kg⁻¹)
Suxamethonium II (1.0 mg kg⁻¹)
0
2
2
4
0
2
4
5
Time (min)

FIG. 1. Time sequence of anaesthesia and administration of drugs.

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TABLE I. *Premedication, dose of atropine and gallamine, number of patients, sex and age distribution in each of the four groups*

Group	I.m. 1 h before induction	I v. 3 min before induction	No. of patients	Male	Mean age (yr) (range)
I	Diazepam 0 1 mg kg^{-1}	Atropine 0.01 mg kg^{-1}	20	13	31.2 (18–57)
II	Diazepam 0.1 mg kg^{-1}	Gallamine 0.3 mg kg^{-1}	20	10	29.6 18–46)
III	Diazepam 0.1 mg kg^{-1} Atropine 0.01 mg kg^{-1}	Gallamine 0.3 mg kg^{-1}	20	13	30.6 (18–52)
IV	Diazepam 0.1 mg kg	Atropine 0.01 mg kg^{-1} Gallamine 0.3 mg kg^{-1}	20	13	32.8 (18–59)
I+II+III +IV			80	49	31.0 (18–59)

eyelash reflex was abolished. Ventilation of the lungs was assisted or controlled throughout the study with halothane 1% in 50% nitrous oxide in oxygen using a non-rebreathing technique.

One minute after the injection of thiopentone was completed and exactly 5 min after, suxamethonium 1 mg kg^{-1} was given i.v. The trachea was not intubated nor surgery performed during the observation period.

Measurements

E.c.g. lead II was monitored continuously throughout the procedure. Heart rate was determined from the e.c.g. (Wisborg, Christensen and Viby-Mogensen, 1977).

Blood samples were taken for measurement of serum potassium concentration, Pa_{CO_2} and Pa_{O_2} before injection of atropine or gallamine, or both, and again 3 min after each injection of suxamethonium. Serum potassium was measured by the flame photometric method and blood-gases measured with a Radiometer ABL 1 acid–base machine. Arterial pressure was recorded every 5 min.

In order to exclude changes in cardiac rate and rhythm caused by gross alterations in Pa_{CO_2}, the results include only those patients in whom Pa_{CO_2} was between 3.3 and 6.7 kPa (25 and 50 mm Hg) throughout the procedure.

Statistical analyses were performed using the χ^2-test, Fisher exact probability test, Kruskal–Wallis test and Wilcoxon matched-paired signed-ranks test. Significance was assigned at a level of 0.05.

RESULTS AND DISCUSSION

Cardiac rate and rhythm

Preinduction period. There were no significant differences between the control values of the groups (fig. 2). After injection of atropine or gallamine, or both, the heart rate increased significantly in all groups ($P < 0.01$). One minute after injection the heart rate in group IV was significantly greater than in other groups.

The maximum changes in heart rate during this period are shown in figure 3. Increases in heart rate to more than 120 beat min^{-1} were found in one patient in group II, in four patients in groups I and III, and in eight patients in group IV. However, these differences were not significant. Five patients in group I, and one patient in group IV had episodes of nodal rhythm after the injection of atropine or gallamine or both.

Induction and first injection of suxamethonium. Only minor changes in heart rate were found after the first injection of suxamethonium. No serious arrhythmia was found. In group I, one patient had nodal rhythm continuing from the period before induction to 30 s after the injection of thiopentone. In group III, two patients developed nodal rhythm 27 and 43 s after the injection of suxamethonium which continued throughout the observation period. The remaining patients had regular sinus rhythm at all times.

Second injection of suxamethonium. After the second injection of suxamethonium, mean heart rate decreased in all groups (fig. 2). The lowest

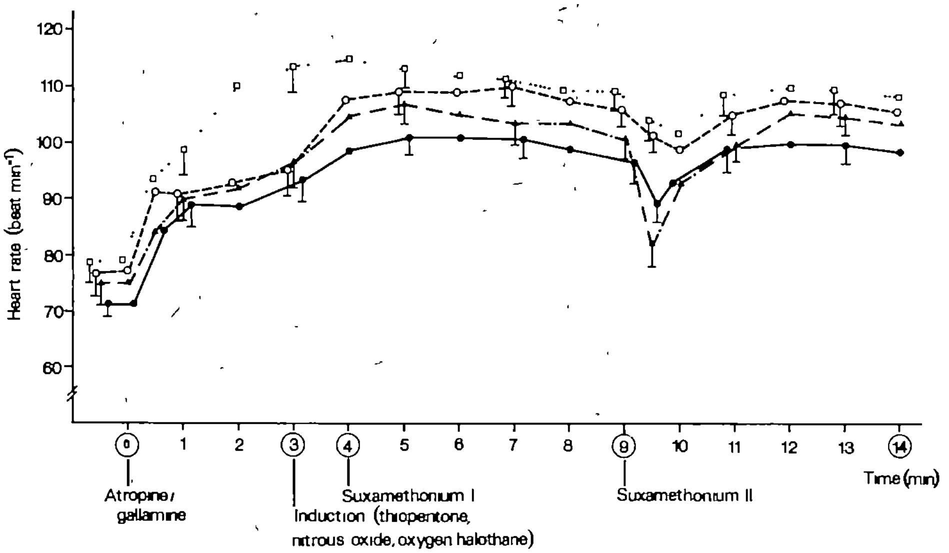

FIG. 2. Heart rate during the observation period. Mean values ± SEM are shown. Group I (atropine 0.01 mg kg^{-1} i.v.) = ▲--▲; group II (gallamine 0.3 mg kg^{-1} i.v.) = ●——●; group III (gallamine 0.3 mg kg^{-1} i.v. and atropine 0.01 mg kg^{-1} i.m.) = ○—○; group IV (gallamine 0.3 mg kg^{-1} i.v. and atropine 0.01 mg kg^{-1} i.v.) = □···□.

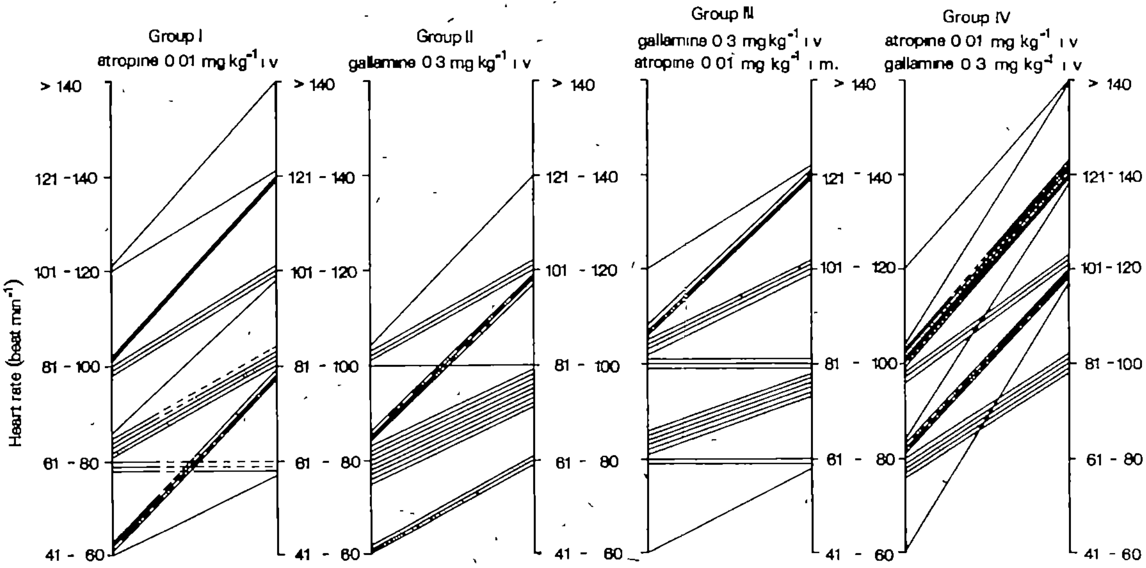

FIG. 3. Maximum changes in heart rate after injection of atropine or gallamine, or both. Each line represents the findings in one patient.— — = Nodal rhythm or nodal extrasystoles.

rates occurred 30 s after injection in groups I and II, and 45 s after injection in groups III and IV. Compared with the values just before injection of the second dose of suxamethonium, the decrease in heart rate was significant only in group I ($P < 0.01$).

Thirty seconds after the second injection of suxamethonium, the heart rates in groups I and II were significantly less than the heart rates in groups III and IV.

The maximum decreases in heart rate after the second injection of suxamethonium are shown in figure 4, with the number of patients who had episodes of nodal rhythm. No patient had serious

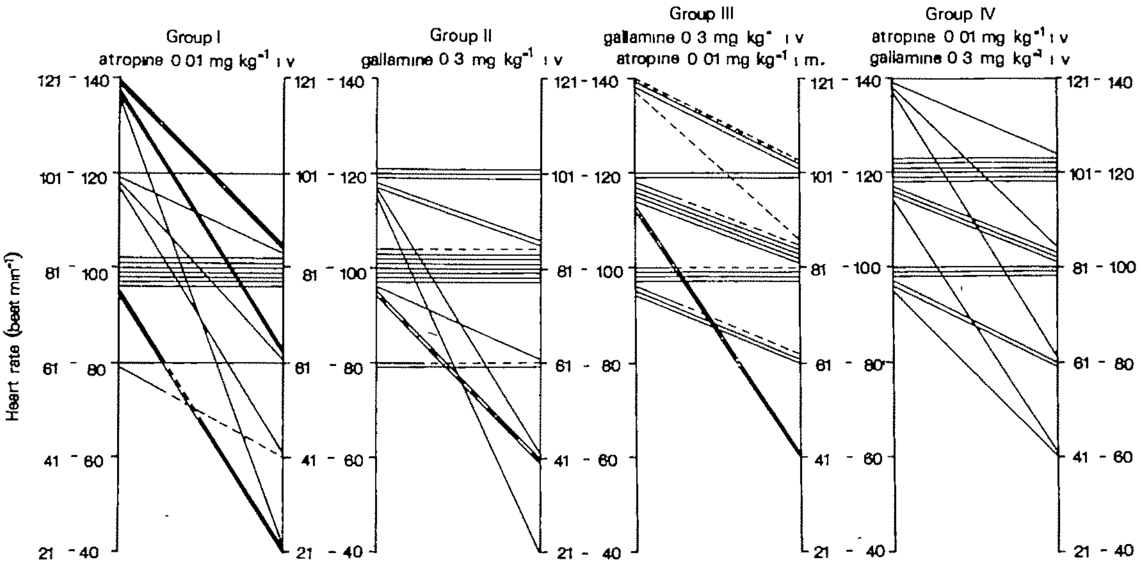

FIG. 4. Maximum decreases in heart rate after second injection of suxamethonium. Each line represents the findings in one patient.--- = Nodal rhythm or nodal extrasystoles.

bradycardia (less than 20 beat min^{-1}) or ventricular arrhythmia.

Pa_{CO_2}, Pa_{O_2} and serum potassium

Only minor variations occurred, and no significant differences were found between the groups.

Arterial pressure

The changes in arterial pressure were small, and no systolic arterial pressure of less than 12 kPa (90 mm Hg) was found.

None of the methods used provided absolute protection against a decrease in heart rate after the second injection of suxamethonium (fig. 4). However, the decrease in heart rate was significant only in group I (atropine 0.01 mg kg^{-1} i.v.) and no patient developed severe bradycardia. Since all four methods investigated were able to protect against extreme bradycardia, we must consider if one method is superior. Both with and without premedication with atropine i.m., gallamine 0.3 mg kg^{-1} i.v. 3 min before the injection of thiopentone provided greater protection. Atropine 0.01 mg kg^{-1} i.v. alone (group I) did not give the same degree of protection (figs 2 and 4) and administration of both atropine and gallamine i.v. (group IV) caused unnecessary tachycardia which could be dangerous in certain patients (Viby-Mogensen et al., 1976).

In earlier similar investigations we found that atropine and gallamine, given during halothane anaesthesia in the same doses used in this investigation, did not provide sufficient protection against severe bradycardia following a second dose of suxamethonium (Viby-Mogensen et al., 1976; Wisborg, Christensen and Viby-Mogensen, 1977). Figures 5, 6, and 7 illustrate the changes in heart rate seen after a second dose of suxamethonium in patients from a previous study who received halothane and nitrous oxide only, compared with changes seen in patients from this investigation in whom thiopentone 4–5 mg kg^{-1} preceded the administration of halothane. The mean heart rate, before the injection of atropine or gallamine, or both, was not significantly different in the four groups. After induction (fig. 5), the mean heart rate was significantly faster in patients who received thiopentone. Forty-five seconds after the second injection of suxamethonium, corresponding to the slowest heart rate in figure 5, the rate was still significantly faster in the patients who received thiopentone. The decrease in heart rate after a second dose of suxamethonium in patients receiving thiopentone was either not significant (gallamine group) or was significantly less (atropine group) than the decrease seen in patients who did not receive thiopentone. None of the patients who received thiopentone developed severe bradycardia (heart rate less than 20

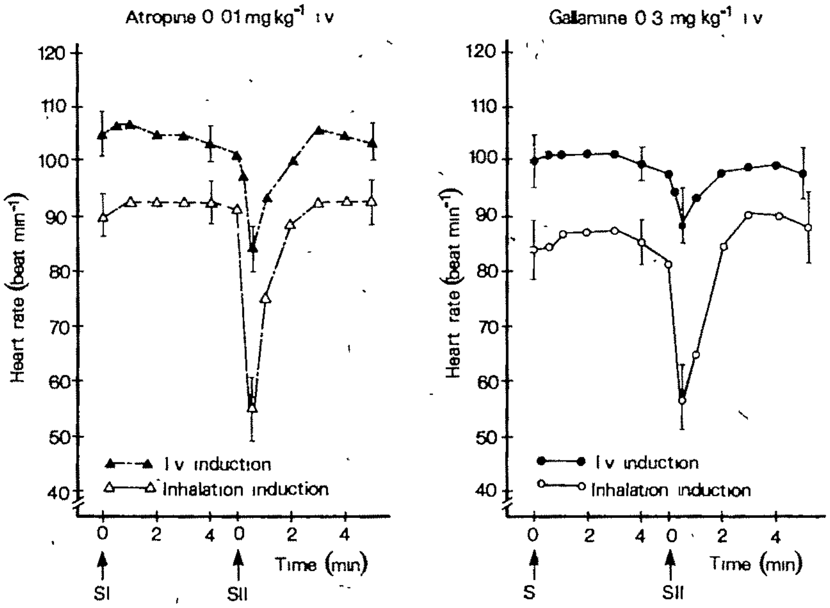

FIG. 5. Significance of thiopentone induction on bradycardia following a repeated dose of suxamethonium during halothane anaesthesia in patients given atropine 0.01 mg kg⁻¹ i.v. or gallamine 0.3 mg kg⁻¹ i.v. before operation. (No. of patients = 80; 20 in each group.) Mean values ± SEM are shown. SI and SII = suxamethonium 1 mg kg⁻¹ i.v. (first and second injection).

beat min⁻¹), whereas four and five patients in the two other groups (figs 6, 7) did so.

There are two possible explanations for the fact that atropine and gallamine in the doses investigated provided sufficient protection against severe bradycardia after a second dose of suxmethonium in patients induced with thiopentone but not in patients induced with halothane and nitrous oxide. The most obvious is that the difference is attributable to the vagolytic properties of thiopentone (Andersen and Eikard, 1978). However, patients in whom anaesthesia was induced with halothane and nitrous oxide were

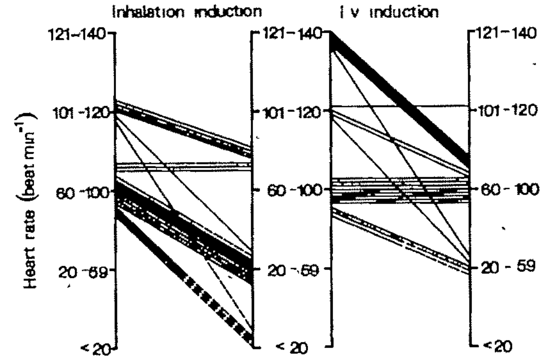

FIG. 6. Maximum decrease in heart rate after second injection of suxamethonium in two groups of patients (20 each) given atropine 0.01 mg kg⁻¹ i.v. and anaesthetized with halothane and nitrous oxide. One group of patients received an inhalation induction, the other received thiopentone 4–5 mg kg⁻¹ i.v. for induction. Each line represents one patient.--- = Nodal rhythm or nodal extrasystoles.

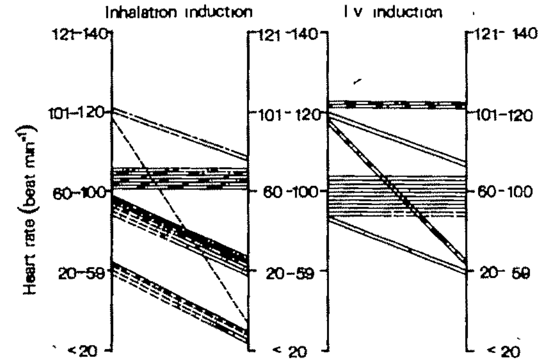

FIG. 7. Maximum decrease in heart rate after second injection of suxamethonium in two groups of patients (20 each) pretreated with gallamine 0.3 mg kg⁻¹ i.v. and anaesthetized with halothane and nitrous oxide. One group of patients received an inhalation induction, the other received thiopentone 4–5 mg kg⁻¹ i.v. for induction. Each line represents one patient.--- = Nodal rhythm or nodal extrasystoles;-·-·- = ventricular extrasystoles.

exposed to halothane for a longer period (10–15 min) at the time of injection of the second dose of suxamethonium than patients induced with thiopentone (5–10 min). Therefore, a more pronounced influence of halothane on the heart cannot be excluded in that group.

ACKNOWLEDGEMENTS

We would like to thank our colleagues in the ENT department (Heads: Professor N Riskær, M.D., G. Salomon, M.D., and Mirko Tos, M D.), the surgical department D (Heads: Tyge Cl. Gertz, M.D. and L Kuld Hansen, M.D.), and the nurses in the anaesthetic department and the operating theatres.

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EFFETS CARDIAQUES DE L'ATROPINE ET DE LA GALLAMINE CHEZ DES MALADES AUXQUELS ON ADMINISTRE DU SUXAMETHONIUM

RESUME

On a réparti quatre-vingts malades sains en quatre groupes au hasard. Avant l'opération, on leur a administré 0,01 mg kg^{-1} d'atropine i.v. (groupe I), 0,3 mg kg^{-1} de gallamine i.v. (groupe II), 0,01 mg kg^{-1} d'atropine i.m. et 0,3 mg kg^{-1} de gallamine i.v. (group III), ou 0,01 mg kg^{-1} d'atropine i v. et 0,3 mg kg^{-1} de gallamine i.v. (group IV). Après les avoir anesthésiés avec de la thiopentone, on leur administra 1 mg kg^{-1} de suxaméthonium i.v. On leur ventila les poumons avec de l'halothane en protoxyde d'azote dans de l'oxygène. On répeta la même dose de suxaméthonium cinq minutes plus tard. Un contrôle du e.c.g. se poursuivit sans arrêt. On n'observa aucune arrythmie grave à la suite de la seconde injection de suxaméthonium dans les groupes I and II. On peut déduire des résultats que la thiopentone protége contre la bradycardie induite par le suxaméthonium au cours de l'anesthésie par halothane

EINWIRKUNGEN VON ATROPIN UND GALLAMIN AUF DAS HERZ VON PATIENTEN, DIE SUXAMETHONIUM BEKOMMEN

ZUSAMMENFASSUNG

Achtzig gesunde Patienten wurden willkürlich in vier Gruppen aufgeteilt. Atropin 0.01 mg kg^{-1} intravenos (Gruppe I), Gallamin 0.3 mg kg^{-1} intravenos (Gruppe II), Atropin 0.01 mg kg^{-} intramuskular und Gallamin 0.3 mg kg^{-1} intravenos (Gruppe III), order Atropin 0.01 mg kg^{-1} intravenös und Gallamin 0.3 mg kg^{-1} intravenös (Gruppe IV) wurden vor der Operation verabreicht. Nach Einleitung der Narkose durch Thiopenton wurde 1 mg kg^{-1} Suxamethonium intravenos verabreicht Die Lungen wurden mit Halothan in Stickstoffoxydul und Sauerstoff beluftet. Fünf Minuten spater wurde dieselbe Dosis Suxamethonium wieder verabreicht. Das EKG wurde ständig überwacht. Nach einer zweiten Injektion von Suxamethonium bei den Gruppen I und II wurde keine ernste Arrhythmie beobachtet. Die Ergebnisse deuten an, dass Thiopenton bei der Halothan-Narkose einen Schutz gegen Suxamethonium-induzierte Bradykardie bietet.

EFECTOS CARDIACOS DE LA ATROPINA Y DE LA GALAMINA EN PACIENTES BAJO ADMINISTRACIÒN DE SUXAMETONIO

SUMARIO

Se distribuyó al azar a ochenta pacientes sanos en cuatro grupos. Antes de la operación, se administró 0,01 mg kg^{-1} de atropina i.v. (grupo I), 0,3 mg kg^{-1} de galamina i.v. (grupo II), 0,01 mg kg^{-1} de atropina i.m. y 0,3 mg kg^{-1} de galamina i.v.(grupo III), ó 0,01 mg kg^{-1} de atropina i v. y 0,3 mg kg^{-1} de galamina i.v. (grupo IV). Después de la inducción de la anestesia mediante tiopentona, se administró 1 mg kg^{-1} de suxametonio i.v. Se ventilaron los pulmones con halotano en óxido nitroso en oxigeno. Se repitió la misma dosis de suxametonio cinco minutos después. Se vigiló continuamente el e.c.g. No se observó arritmia grave después de la segunda inyección de suxametonio en los grupos I y II. Los resultados sugieren que la tiopentona protege contra la bradicardia inducida por el suxametonio durante la anestesia por halotano.

Br. J. Anaesth. (1980), 52, 1143

BLOOD CONCENTRATIONS OF NITROUS OXIDE IN THEATRE PERSONNEL

J. R. KRAPEZ, Y. SALOOJEE, C. J. HINDS, G. H. HACKETT AND P. V. COLE

SUMMARY

Blood concentrations of nitrous oxide were measured in anaesthetists, surgeons and theatre nurses. Comparison of anaesthetists and surgeons working in the same theatre showed that in ENT surgeons concentrations were greater ($P < 0.01$), while in general surgeons they were smaller ($P < 0.003$). Blood concentrations of nitrous oxide in the "circulating" nurses were low, with scavenging they were unmeasurable. Atmospheric concentrations in the breathing zones were usually greater than the corresponding blood concentrations, but this was not always true. However, a positive correlation between blood and atmospheric concentrations was obtained ($r = 0.82$). Meticulous use of scavenging devices produced a mean reduction in blood nitrous oxide concentrations of 86% for all groups. The mean blood concentration of nitrous oxide in anaesthetists when scavenging was used was 45 p.p.m. (1.9 μmol litre^{-1}). This figure should be taken into account in establishing maximum permitted exposure to nitrous oxide.

The measurement of nitrous oxide has been recommended as the basis for environmental monitoring of operating theatre pollution (NIOSH, 1977). This gas forms a part of most anaesthetic techniques and is the most abundant pollutant in theatre atmospheres. Measurement of nitrous oxide also provides a means of estimating the degree of exposure to any volatile adjuvant.

Although several studies of theatre pollution with nitrous oxide have been published (Linde and Bruce, 1969; Davenport et al., 1976; Piziali et al., 1976), there is limited information on the absorption of this agent by theatre personnel. Studies which measured the uptake of nitrous oxide by subjects working in the operating theatre have used end-tidal sampling (Nikki, Pfaffli and Ahlman, 1973; Mehta, Burton and Sims, 1978). However, in the assessment of individual exposure to an environmental pollutant, the method of choice is the measurement of blood concentration (Astrup, 1973). While trace concentrations of nitrous oxide in blood have been reported (Kortilla, Pfaffli and Ertama, 1978; Kortilla et al., 1978), the measurements were only carried out on subjects after they had left the operating theatre.

We have investigated the relationship between nitrous oxide concentrations in the environment and the "real" exposure of theatre personnel represented by venous blood concentrations. The effects of scavenging and theatre ventilation on these concentrations were also studied.

METHODS

Anaesthetists, surgeons and "circulating" nurses were studied during routine operating lists. The exposure of anaesthetists was assessed in three different operating theatres, the ventilation characteristics of which are given in table I. The surgeons studied were carrying out either ENT (theatre 3) or general surgical procedures (theatre 2) and the circulating nurses were working in theatre 1. The effectiveness of passive scavenging in reducing pollution was also determined for all groups.

The anaesthetic circuits used were a Mapleson A or a "Manley" ventilator and the flow rate of nitrous oxide was standardized at 6 litre min^{-1}. Scavenging was carried out with a commercial scavenging valve (M. and I. E. Limited) or directly from the exit port of the ventilator. Waste gases were conducted from anaesthetic room and operating theatre to the outside air via wide-bore plastic tubing.

Samples of venous blood were taken at hourly intervals from anaesthetists and nurses and from surgeons at the end of each operation. Heparinized

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0007-0912/80/111143-06 $01.00

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TABLE I *Ventilation characteristics of theatres studied*

Theatre	Main surgical procedure	Theatre size (m)	Air changes per hour	Ventilation type
1	Gynaecological	7.62 × 6.10 × 3.36	14.9	Turbulent flow
2	General	7.62 × 5.79 × 4.15	6.4	Turbulent flow
3	ENT	6.25 × 5.49 × 3.05	12.9	Downward displacement

gas-tight "Hamilton" syringes were used to obtain the samples. Care was taken to exclude air bubbles and the needle was sealed by insertion into a rubber stopper. At the same time, atmospheric samples were taken from the subject's breathing zone (15–23 cm from the nose) over 60 s using a diaphragm pump and collected into polythene gas-sampling bags (Hawkins, 1967). The samples were analysed using a gas chromatograph (Perkin–Elmer F17) equipped with a micro-ionization cross-section detector and a Porapak Q column. Nitrous oxide was extracted from the blood using the "vortex extraction" technique. This method has been fully described elsewhere (Saloojee and Cole, 1978).

RESULTS

Exposure of anaesthetists, surgeons and nurses

The mean blood and breathing zone concentrations of nitrous oxide for all groups are shown in table II. No measurable concentrations of nitrous oxide were found in the blood of any of the groups before exposure. The exposure of personnel when working in unscavenged theatres was analysed by the Mann–Whitney *U* test. A comparison of blood nitrous oxide concentrations for surgeons and anaesthetists working in the same theatres showed the values to be greater in ENT surgeons ($P<0.01$) and smaller in general surgeons ($P<0.003$). Breathing zone concentrations were not significantly different between anaesthetists and ENT surgeons, but were significantly less for general surgeons ($P<0.05$). Circulating nurses were the least exposed group. Both their blood and atmosphere concentrations were much lower than either anaesthetists' or surgeons'. A regression line was obtained from a comparison of blood with atmosphere concentrations for all groups studied and is shown in figure 1 ($r = 0.82$; $n = 116$; $P<0.001$). Blood concentrations less than 0.85 μmol litre^{-1} (the limit of resolution of our technique) and their corresponding atmospheric values were not included in the regression analysis.

TABLE II. *Exposure of operating room personnel.* n = *Number of samples*

		Mean (range) blood concns (μmol litre^{-1})		Mean (range) atmosphere (p.p.m.)	
	Theatre	No precautions	Passive scavenging	No precautions	Passive scavenging
Anaesthetists	1	14.9 (3.4–50.2) $n = 17$	2.1 (<0.9–4.6) $n = 12$	721 (96–2001) $n = 17$	79 (15–203) $n = 12$
	2	13.3 (3.1–45.5) $n = 22$	1.3 (<0.9–2.9) $n = 12$	591 (52–2385) $n = 22$	41 (8–112) $n = 12$
	3	6.3 (4.3–12.7) $n = 15$	<0.9 (<0.9–1.2) $n = 10$	227 (78–676) $n = 15$	35 (6–72) $n = 10$
Surgeons	2	4.2 (2.6–6.1) $n = 8$	<0.9 (<0.9–0.9) $n = 9$	170 (133–194) $n = 5$	34 (3–125) $n = 9$
	3	16.8 (2.2–34.1) $n = 8$	2.0 (<0.9–8.8) $n = 8$	716 (96–1931) $n = 8$	74 (25–207) $n = 8$
Nurses	1	2.9 (0.9–8.3) $n = 16$	<0.9 (All below 0.9) $n = 12$	93 (23–203) $n = 15$	19 (8–75) $n = 12$

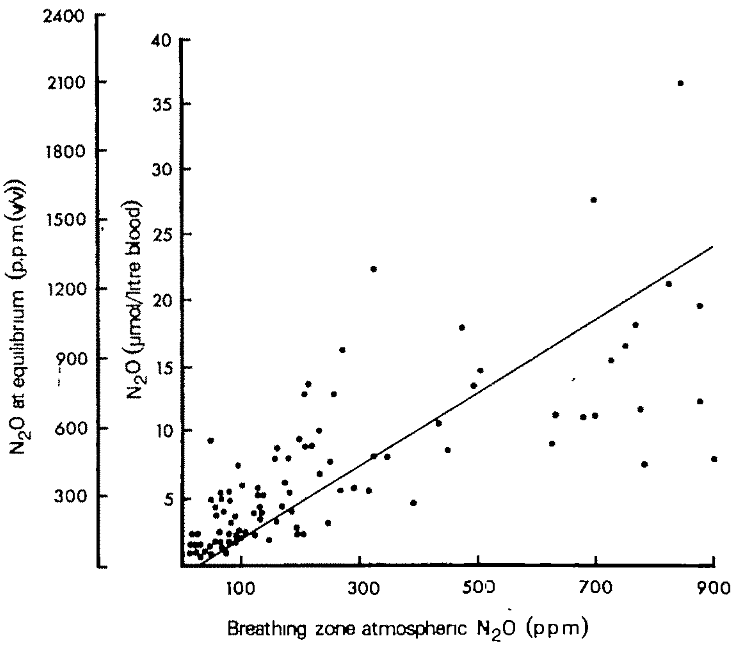

FIG. 1. Correlation between blood and breathing zone atmosphere concentrations of nitrous oxide. The alternative scale indicates the parts per million (v/v) of dry nitrous oxide inhaled until equilibrium which would give the corresponding blood concentration (assuming blood–gas partition coefficient = 0.47, arterial pressure = 101.8 kPa, body temperature = 37 °C).

Scavenging

The passive scavenging of expired anaesthetic gases produced a mean reduction of 86% in exposure of all personnel in the operating theatre. Most blood samples obtained from general surgeons and nurses contained nitrous oxide concentrations less than the limit of resolution of the gas chromatographic system. Higher mean concentrations were found in anaesthetists and ENT surgeons (table II) with occasional extremely high concentrations attributable to leaks from around the face-mask.

Theatre ventilation

Figure 2 analyses the data obtained from anaesthetists in each of the three theatres studied. There was no significant difference in the concentrations of nitrous oxide measured in either blood or atmosphere when comparing the two theatres (1 and 2) with turbulent flow ventilation. In theatre 3, with a downward displacement ventilation system, both concentrations were significantly decreased ($P<0.025$ without scavenging; $P<0.05$ with scavenging).

DISCUSSION

The exposure of theatre personnel to pollutants depends on several factors. These include non-uniform distribution of theatre ventilation and the release of waste gases from a point-source, both of which lead to the production of zones of differing degrees of pollution within the operating suite. Consequently, movement of personnel will affect the amount of waste anaesthetic gas absorbed. In addition, equilibrium between the atmosphere and the subject is seldom achieved. The problem of quantifying chronic exposure in terms of atmospheric concentrations is thus prohibitively complex.

We have determined the real occupational exposure of anaesthetists, nurses and surgeons to nitrous oxide and its relation to the ambient gas concentrations in the theatre environment. Of these groups, the ENT surgeons had the greatest exposure. Surgeons in this specialty work close to the expiratory valve and are thus continuously exposed to high concentrations of pollutants during the surgical procedure. Their anaesthetic

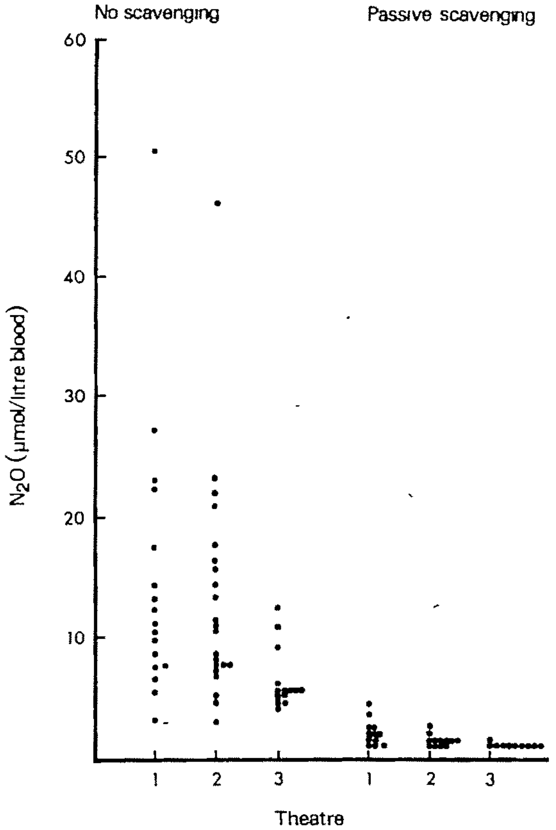

FIG 2 The range of blood nitrous oxide concentrations measured in anaesthetists in each of the three theatres with and without scavenging.

colleagues, while exposed to similar environmental nitrous oxide concentrations, had lower blood concentrations. The most likely explanation for this disparity is the relative mobility of the anaesthetists, who therefore have a less continuous exposure to the greatest concentrations. General surgeons, who are usually further removed from the airway, had lower nitrous oxide concentrations than both these groups. An assessment of background theatre pollution is afforded by the measurements on the "circulating" nurses and this was found to be uniformly low even in the absence of scavenging.

The atmospheric concentrations sampled from the breathing zone of anaesthetists (range 52–2385 p.p.m., mean 534 unscavenged; 6–203 p.p.m., mean 57 scavenged) are comparable to those reported elsewhere (Levy, 1975; Kortilla et al., 1978). There was a positive correlation between blood and atmospheric concentrations of nitrous oxide ($r = 0.82$), but on several occasions atmospheric concentrations were smaller than the corresponding blood value. On average only 68% of an individual's true exposure (the blood concentration) could be attributed to the atmospheric concentration of nitrous oxide.

The median blood nitrous oxide concentration in anaesthetists showed less variation than the corresponding atmospheric concentrations (fig. 3). Analysis of variance for blood and atmospheric samples at each measurement interval revealed significant differences ($P<0.001$ at 1.3 and 4 h; $P<0.01$ at 2 h). This suggests that the measurement of blood concentrations provides some degree of integration of the subject's exposure. This conflicts with statements made by other workers (Davenport et al., 1977) who considered blood nitrous oxide concentrations to reflect the most recent exposure.

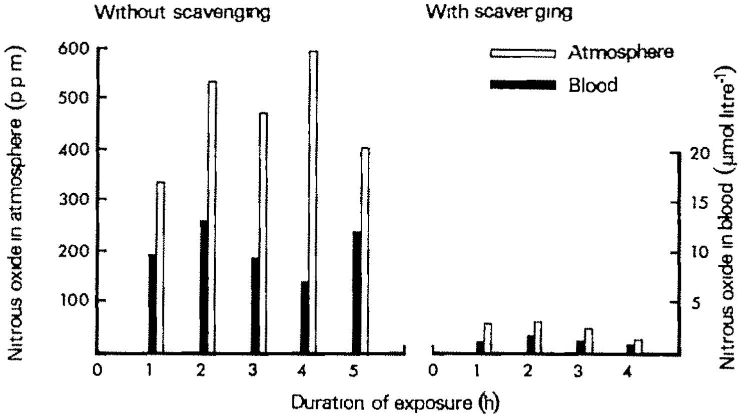

FIG. 3. The median blood and atmosphere nitrous oxide concentration for anaesthetists at each measurement interval

The effectiveness of passive scavenging in this study was primarily because of the meticulous care taken to avoid pollution. Such obsessional use of scavenging may not only be impractical in routine clinical work but could also interfere with patient care. For example, complete elimination of leakage around the face-mask would require routine endotracheal intubation. Marked alterations in anaesthetic techniques would be necessary if the recommended maximum average atmospheric concentrations (25 p.p.m.) of the NIOSH report (1977) are to be implemented. We do not believe that the required changes would be in patients' best interests, and we suggest that this figure needs revision. The mean value for blood nitrous oxide concentrations in anaesthetists when scavenging was 45 p.p.m. ($1.9\ \mu mol\ litre^{-1}$). We suggest this should form the basis for a recommended maximum average exposure, care being required to achieve even this value. Such a figure would be approximately equivalent to an atmospheric concentration of 100 p.p.m.

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CONCENTRATIONS DU PROTOXYDE D'AZOTE DANS LE SANG DU PERSONNEL OPERATOIRE

RESUME

On a mesuré les concentrations du protoxyde d'azote dans le sang d'anesthésistes, de chirurgiens et d'infirmières travaillant dans des salles d'operation. En comparant les résultats relatifs aux anesthésistes et aux chirurgiens d'une même salle d'operations, on a remarqué que les concentrations étaient plus élevées ($P<0,01$) chez les chirurgiens ENT et qu'elles étaient moins fortes chez les chirurgiens de chirurgie générale ($P<0,003$). Les concentrations du protoxyde d'azote dans le sang des infirmières "circulantes" étaient faibles; il n'était pas possible de les mesurer là où le nettoyage s'effectuait. Les concentrations atmosphériques dans les zones de respiration étaitent habituellement plus élevées que les concentrations correspondantes dans le sang, mais il n'en était pas toujours ainsi. Toutefois, on a pu établir une corrélation positive entre les concentrations atmosphériques et sanguines ($r = 0.82$). L'utilisation méticuleuse de dispositifs de nettoyage eut pour résultat une réduction moyenne des concentrations du protoxyde d'azote dans le sang de 86% dans tous les groupes. Lorsque des procédés de nettoyage étaient en usage, la concentration moyenne du protoxyde d'azote dans le sang des anesthésistes s'élevait à 45 p.p.m. ($1,9\ \mu mol\ litre^{-1}$). Il convient de tenir compte de ce chiffre au moment de fixer l'exposition maximale au protoxyde d'azote permise.

BLUTKONZENTRATIONEN VON STICKSTOFFOXYDUL BEI OPERATIONSRAUM-PERSONNAL

ZUSAMMENFASSUNG

Blutkonzentrationen von Stickstoffoxydul bei Anästhetisten, Chirurgen und Operationsraum-Krankenschwestern wurden gemessen. Ein Vergleich zwischen Anästhetisten und Chirurgen, die im selben Operationsraum arbeiteten, zeigte, dass bei Hals-Nasen-Ohren-Chirurgen die Konzentrationen stärker ($P<0.01$) aber bei allgemeinen Chirurgen kleiner waren ($P<0.003$). Blutkonzentrationen von Stickstoffoxydul waren gering bei den "zirkulierenden" Krankenschwestern; bei Anwendung von Spulmassnahmen waren sie unmessbar. Atmosphärische Konzentrationen in den Atmungszonen waren gewöhnlich grösser als die entsprechenden Blutkonzentrationen, aber das war nicht immer der Fall. Es wurde jedoch eine postive Korrelation zwischen Blutkonzentrationen und atmosphärischen Konzentrationen festgestellt ($r = 0.82$). Äusserst sorgfältige Verwendung von Spülvorrichtungen führte zu einer durschnittlichen Reduktion der Blutstickstoffoxydul-Konzentrationen für alle Gruppen um 86%. Die durchschnittliche

Blutstickstoffoxydul-Konzentration bei Anasthetisten bei Verwendung von Spülvorrichtungen war 45 p.p.m. (1,9 μmol litre^{-1}). Diese Zahl sollte bei der Aufstellung von maximal zulassigen Stickstoffoxydul-Aussetzungszeiten in Betracht gezogen werden.

CONCENTRACIONES DE OXIDO NITROSO EN LA SANGRE DEL PERSONAL OPERATORIO

SUMARIO

Se midió las concentraciones de óxido nitroso en la sangre de anestesistas, cirujanos y enfermeras que trabajan en salas de operaciones. Al comparar a los anestesistas y cirujanos de la misma sala, se comprobó que las concentraciones eran mayores en los cirujanos ENT ($P<0,01$) y menores en los cirujanos de cirujia general ($P<0,003$). Las concentraciones de óxido nitroso en la sangre de las enfermeras "circulantes" eran bajas; cuando se usaba un proceso de limpieza, no se podía medirlas. Las concentraciones atmosféricas en las zonas de respiración solian ser mayores que en las concentraciones sanguíneas correspondientes; no obstante, no era siempre así. Sin embargo, se obtuvo una correlación positiva entre las concentraciones atmosféricas y las sanguíneas ($r = 0,82$). El uso meticuloso de dispositivos de limpieza llevó consigo una disminución promedia del 86% de las concentraciones de óxido nitroso en la sangre de todos los grupos. Al usar dispositivos de limpieza, la concentración promedia de óxido nitroso en la sangre de los anestesistas alcanzaba 45 p.p.m. (1,9 μmol litre^{-1}). Cabe tener en cuenta esta cifra al fijar los niveles máximos de exposición al óxido nitroso permitidos.

Br. J. Anaesth. (1980), 52, 1149

PROLONGATION OF SUXAMETHONIUM FOLLOWING PLASMA EXCHANGE

J. LUMLEY

SUMMARY

Repeated plasma exchange was used in the treatment of a 70-yr-old man with Wegener's granulomatosis Two days following the last exchange, the plasma cholinesterase was 14% of normal and there was a prolonged response to the action of suxamethonium

Repeated plasma exchange is an established method of treatment for acute antibody-mediated and immune-complex diseases (Pinching, 1979). During the procedure, the removed plasma is replaced with a colloid or crystalloid solution, resulting in a temporary reduction in the concentration of normal plasma constituents. Thus, a decrease in cholinesterase concentration could be expected to result in prolonged action of suxamethonium. Recently, the author had an opportunity to verify this hypothesis.

CASE REPORT

The patient was a 70-yr-old man weighing 80 kg, with a 10-year history of rheumatoid arthritis which had been treated with phenylbutazone, ibuprofen and indomethacin. For 3 months before admission to Hammersmith Hospital, London, he had a history of dyspnoea, recurrent haemoptysis, and a diagnosis of nephritis had been made. His condition improved following treatment with prednisolone. The provisional diagnosis on admission was Wegener's granulomatosis or Goodpasture's syndrome and he was given prednisolone 200 mg daily and cyclophosphamide 60 mg daily. Daily plasma exchange was carried out, on each occasion 4 litre being removed and replaced mainly with plasma protein fraction. Following the ninth plasma exchange, the patient had an epistaxis and a granuloma was found on the nasal septum. A biopsy was performed 2 days after the 13th plasma exchange. Following the last exchange 2 units of blood had been given. On the day of the operation, the plasma cholinesterase concentration was 499 u. litre^{-1}. This was assayed by the method described by Wood and Hall (1978); normal mean values for the assay were 3637 u. litre^{-1}(SEM $\pm$ 226) in 22 normal patients. Premedication consisted of lorazepam 4 mg orally, and hydrocortisone 100 mg and atropine 1.2 mg were given i.v. before induction. Following a sleep-dose of methohexitone, anaesthesia was maintained with nitrous oxide in oxygen via a Magill circuit, with incremental doses of methohexitone 10–20 mg as needed.

The ulnar nerve was stimulated supramaximally at the elbow at a frequency of 0.5 Hz and stimulus duration 0.1 ms using a Palmer stimulator. The twitch response of the adductor pollicis was recorded on a Devices recorder using a Grass strain gauge. Following 2 min of stimulation, suxamethonium 80 mg was given, the recording being continued. During the period of paralysis the trachea was intubated with a cuffed tube.

The response to ulnar nerve stimulation reappeared 23.5 min after administration of suxamethonium and had reached control height after 30.25 min. The patient's permission had been sought to carry out this investigation.

DISCUSSION

Wood and Hall (1978) have shown that a single 4-litre plasma exchange can remove about 64% of plasma cholinesterase. Repeated daily plasma exchanges virtually removes cholinesterase and Patterson, Walsh and Hall (1979) suggest caution in the use of drugs known to be metabolized by the enzyme.

The duration of action of suxamethonium is thought to be prolonged when the enzyme concentration is less than 20% of normal (Vickers,

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0007-0912/80/111149-02 $01.00

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Wood-Smith and Stewart, 1978). The concentration in this patient was 14% of normal 2 days following the last plasma exchange and immediately before operation. This cholinesterase value of 499 u. litre^{-1} was greater than might be anticipated because of the transfusion of 2 units of blood after the last exchange, a manoeuvre which is known to increase the enzyme concentration (Patterson, Walsh and Hall, 1979). Although figures have been quoted for the half-life of cholinesterase, these have been calculated following infusion of the enzyme into subjects with no cholinesterase activity, and the rate of regeneration of cholinesterase following plasma exchange is not known.

In view of this fact, it is surprising that Evans, Macdonald and Robinson (1980) assumed that cholinesterase concentrations would be close to normal limits by the time of delivery in a pregnant patient who had undergone seven plasmaphoreses in 3 weeks. A significant reduction in cholinesterase concentration has been demonstrated during the first trimster, to concentrations which are maintained during the remainder of gestation (Evans and Wroe, 1979). In this patient, therefore, there were two reasons for suspecting reduced cholinesterase concentrations before Caesarean section under general anaesthesia. A depolarizing block was confirmed by the use of a peripheral nerve stimulator and cholinesterase concentrations were measured retrospectively.

This author agrees with their recommendation that cholinesterase concentrations should be measured before operation in patients who have undergone repeated plasma exchanges.

However, the low concentration of cholinesterase found under these conditions is not an absolute contraindication to the use of suxamethonium, but prolonged action of the drug is to be expected and appropriate measures taken.

ACKNOWLEDGEMENTS

The author wishes to thank Mr M. K. Chakrabarti and Miss J. Patterson for technical assistance, Drs G. Hall and M. Morgan for advice and interest and Miss G. Mead for secretarial assistance.

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PROLONGATION DE L'EFFET DU SUXAMETHONIUM APRES ECHANGE DE PLASMA

RESUME

On a, pour le traitement d'un homme âgé de 70 ans souffrant d'une granulomatose de Wegener, procédé à des échanges de plasma répétés. Deux jours après le dernier échange, la cholinestérase du plasma était revenue à 14% de la normale, et il y a alors eu une réaction prolongée à l'action du suxaméthonium.

WIRKUNGSVERLÄNGERUNG VON SUXAMETHONIUM NACH PLASMAAUSTAUSCH

ZUSAMMENFASSUNG

Wiederholter Plasmaaustausch wurde in der Behandlung eines 70jährigen Mannes mit Wegeners Granulomatose durchgeführt. Zwei Tage nach dem letzten Austausch betrug die Plasma-Cholinesterase 14% des Normalwertes, und es bestand eine verlängerte Reaktion auf die Wirkung von Suxamethonium.

PROLONGACION DEL SUXAMETONIUM DESPUES DEL INTERCAMBIO DE PLASMA

SUMARIO

En el tratamiento de un hombre de 70 años con granulomatosis de Wegener se empleó de forma repetitiva intercambio de plasma. A los dos dias de efectuado el último intercambio, la colinesterasa del plasma fue del 14% en relación a la cantidad normal y hubo una prolongada respuesta a la actividad del suxametonium.

Br. J. Anaesth. (1980), 52, 1151

ACUTE HEPATITIS FOLLOWING ENFLURANE ANAESTHESIA

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J. BOTHA AND M. C. KEW

SUMMARY

A patient developed fever and acute hepatitis shortly after enflurane anaesthesia. Other causes of postoperative hepatitis were excluded. Cross-sensitization with halothane may have occurred, and the enflurane hepatitis may have been aggravated by halothane hepatitis.

Hepatitis may occur after single, or more usually repeated, exposures to the halogenated anaesthetic agents halothane (Moult and Sherlock, 1975), methoxyflurane (Joshi and Conn, 1974) and fluroxene (Harris and Cromwell, 1972). Hypersensitivity to these agents is probably the mechanism responsible for this rare complication, and cross-sensitization between the various fluorinated anaesthetic agents may occur (Judson, de Jongh and Walmsley, 1971; Sadove and Kim, 1974; Moult and Sherlock, 1975). Enflurane also might be expected to produce hepatitis and, indeed, a few cases of mild hepatic damage associated with its use have been reported (Sadove and Kim, 1974; Tsang, 1975; Ona, Patanella and Ayub, 1980). We describe a patient in whom more severe hepatitis developed after enflurane anaesthesia.

CASE REPORT

An obese 47-yr-old businessman was transferred from a country hospital to the Johannesburg Hospital following a shooting accident involving his left arm. His brother, a medical practitioner, had applied a tourniquet to the arm immediately after the injury and injected morphine 15 mg i.v. He measured the patient's arterial pressure frequently and at no stage did hypotension occur. Five hundred millilitre of fully cross-matched blood was transfused at the country hospital.

The patient had undergone a subtotal thyroidectomy 4 years previously under halothane anaesthesia. There was no previous exposure to enflurane, methoxyflurane or fluroxene. He was allergic to penicillin. There was no history of liver disease, alcohol abuse or contact with hepatitis.

On admission to the Johannesburg Hospital 6 h after the accident, the patient was not shocked. His left arm was shattered and an emergency above-elbow amputation was carried out. No premedication was given. Anaesthesia was induced with droperidol 5 mg and fentanyl 200 μg followed by thiopentone 150 mg, all i.v. Enflurane 1.5% in 50% nitrous oxide in oxygen delivered by intermittent positive pressure ventilation was given to maintain anaesthesia after tracheal intubation. The course of anaesthesia, which lasted for 90 min, was uneventful and at no stage during or after the operation did systemic hypotension occur. A leucocyte count of 20 500 m^{-3} was the only abnormal laboratory test on admission. Of particular relevance, liver function tests and prothrombin time were normal at this time. A few hours after operation pyrexia developed, and over the next 3 days temperatures as high as 38.5 °C were recorded. On the 4th day after operation the serum aminotransferase concentrations were noted to be increased (alanine aminotransferase (ALT) 690 iu $litre^{-1}$ and aspartate aminotransferase (AST) 575 iu $litre^{-1}$). The serum bilirubin concentration was normal.

Hepatitis-B surface antigen was not found in the patient's serum (nor was anti-HBs detected in his serum several months later). Repeated blood and urine cultures and culture from swabs of the amputation wound yielded no growth. There was no increase in the serum urea or creatinine concentrations after operation, and the patient's

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0007-0912/80/111151-03 $01.00

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urine did not contain protein, casts or excessive numbers of cells. Change of dressing and inspection of the wound under anaesthesia were carried out on the 4th day. The patient was premedicated with papaveretum 20 mg and promethazine 50 mg i.m. 1 h before operation. Anaesthesia was induced with thiopentone and maintained with halothane in nitrous oxide with oxygen. The patient was apyrexial after operation but the following day a temperature of 40 °C was recorded.

Serum bilirubin concentration was increased to 28 mmol litre^{-1} and ALT was now 2580 iu litre^{-1} and AST 1880 iu litre^{-1}. ALT and bilirubin concentrations continued to increase, reaching a maximum of 6840 iu litre^{-1} and 89 mmol litre^{-1} respectively, on the 7th day; the prothrombin time was 44% and the serum albumin concentration 31 g litre^{-1}. Thereafter liver function tests improved. Formal closure of the amputation stump was performed under brachial plexus block on the 18th day. A liver biopsy was not performed. At this stage the patient had no fever and had recovered clinically. Liver function returned to normal after 2 month.

DISCUSSION

Our patient developed fever and biochemical evidence of liver damage 4 days after being anaesthetized with enflurane and he became jaundiced 2 days later. Other causes of jaundice after operation, such as septicaemia, hypoxia, non-anaesthetic drugs, pre-existing liver disease and virus hepatitis were excluded. Calverley and colleagues (1978) have shown that enflurane 1.68% given by intermittent positive pressure ventilation to patients whose mean age was 39 yr may produce systemic hypotension. However, our patient's arterial pressure was maintained throughout the course of the operation and the period after operation. Moreover, it might be expected that hypotensive damage to the liver would have been accompanied by renal ischaemia, and no evidence for the latter was found. Therefore, the patient was thought to have developed hepatitis attributable to enflurane.

The clinical features of enflurane hepatitis appear to be similar to those of halothane (Moult and Sherlock, 1975), methoxyflurane (Joshi and Conn, 1974) and fluroxene hepatitis (Harris and Cromwell, 1972). Fever has occurred as early as 4 h after operation and as late as the 4th day (Judson, de Jongh and Walmsley, 1971; Denlinger, Lecky and Nahrwold, 1974; Sadove and Kim, 1974; Tsang, 1975). Jaundice, when present, has followed from 1 to 9 days later (Judson, de Jongh and Walmsley, 1971; Denlinger, Lecky and Nahrwold, 1974; Sadove and Kim, 1974; Tsang, 1975). Apart from one patient (Van Der Reis et al., 1974) in whom pre-existing cirrhosis was present and who died in hepato-renal failure 20 days after exposure to enflurane, the other patients reported appear to have suffered only mild or relatively mild liver damage. Although this patient showed no clinical signs of liver failure, his serum aminotransferase concentration reached 6840 iu litre^{-1}, his serum bilirubin concentration 89 mmol litre^{-1}, and his prothrombin time 44%, and it took 2 months for liver function to return to normal. Eosinophilia has been present in some, but not all, of the reported patients (Denlinger, Lecky and Nahrwold, 1974; Sadove and Kim, 1974). Obesity seems to predispose to halothane (Moult and Sherlock, 1975) and methoxyflurane hepatitis (Joshi and Conn, 1974), and our patient was obese also.

Cross-sensitization between halothane and enflurane (Sadove and Kim, 1974) and methoxyflurane and halothane (Joshi and Conn, 1974) may occur and cross-stimulation of lymphocyte transformation has been demonstrated (Paronetto and Popper, 1970). The halothane that our patient received 4 yr previously might have sensitized him to enflurane. The day after fever and increase in serum aminotransferase concentrations developed, this patient was again exposed to halothane and this could have aggravated the hepatitis.

Enflurane is chemically stable and undergoes slow biotransformation (Harrison et al., 1976). It is not itself hepatotoxic (Chase et al., 1971) and metabolism in the liver apparently does not produce toxic metabolites (Harrison et al., 1976). It is conceivable, however, that prior sensitization by a different halogenated agent may modify the normal biotransformation system and result in the production of toxic metabolites.

We believe that unexplained fever and increases in serum aminotransferases with or without jaundice after enflurane anaesthesia are contraindications to further exposure to enflurane or other halogenated agents.

ACKNOWLEDGEMENTS

The authors wish to thank the Superintendent of the Johannesburg Hospital, Dr N. E. Howes, for permission to publish this case report.

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HEPATITE AIGUE A LA SUITE DE L'ANESTHESIE A L'ENFLURANE

RESUME

Peu après avoir été anesthésié à l'enflurane, un patient a eu de la fièvre et souffert d'hépatite aigüe. Toutes autres causes d'hépatite postopératoire ont été exclues. Il se peut qu'une sensibilisation croisée avec l'halothane se soit produite et l'hépatite due à l'enflurane s'est peut-être aggravée en raison de l'hépatite causée par l'halothane.

AKUTE HEPATITIS NACH ENFLURAN-NARKOSE

ZUSAMMENFASSUNG

Bei einem Patienten traten kurz nach einer Enfluran-Narkose eine Fieber und akute Hepatitis ein. Andere Ursachen von postoperativer Hepatitis wurden ausgeschlossen. Kreuzsensibilisierung mit Halothan könnte vielleicht vorgekommen sein, und die Enfluran-Hepatitis konnte eventuell durch Halothan-Hepatitis erschwert worden sein.

HEPATITIS AGUDA DEPUES DE LA ANESTESIA CON ENFLURANO

SUMARIO

Un paciente tuvo fiebre y hepatitis aguda poco después de la anestesia por enflurano. Se excluyeron las demás causas de hepatitis postoperatoria. Pueda haber sucedido una sensibilización cruzada con el halotano, y la hepatitis a raíz del enflurano puede haber empeorado por causa de la hepatitis por halotano.

Br. J. Anaesth. (1980), 52, 1155

AN IMPROVED ULTRA-VIOLET HALOTHANE METER

K. V. DIPROSE, H. G. EPSTEIN AND L. R. REDMAN

SUMMARY

The development of an ultra-violet absorption meter, suitable for the measurement of concentrations of halothane (0–5%) under clinical conditions, is described. The scale is accurate to 0.05% and the zero drift did not exceed 0.25% halothane over 15 h after a 5-min warm-up period. The inherent time of response is about 2 s.

Halothane absorbs ultra-violet light at wavelengths less than 270 nm with a peak absorption at approximately 200 nm. A simple ultra-violet absorption photometer, suitable for estimating those concentrations used in clinical anaesthesia, was developed by Robinson, Denson and Summers (1962) and marketed by Hook and Tucker Ltd. More recently, a rapid-response ultra-violet halothane meter system, suitable for direct incorporation in an anaesthetic breathing system has been developed by Tatnall, West and Morris (1978).

The working principles of the original Hook and Tucker design are shown in figure 1. This design suffered from two major faults: sensitivity changed with time and zero was unstable. The change in sensitivity was primarily a result of the increase in the ultra-violet output from the lamp with the increase in mercury vapour pressure as the lamp

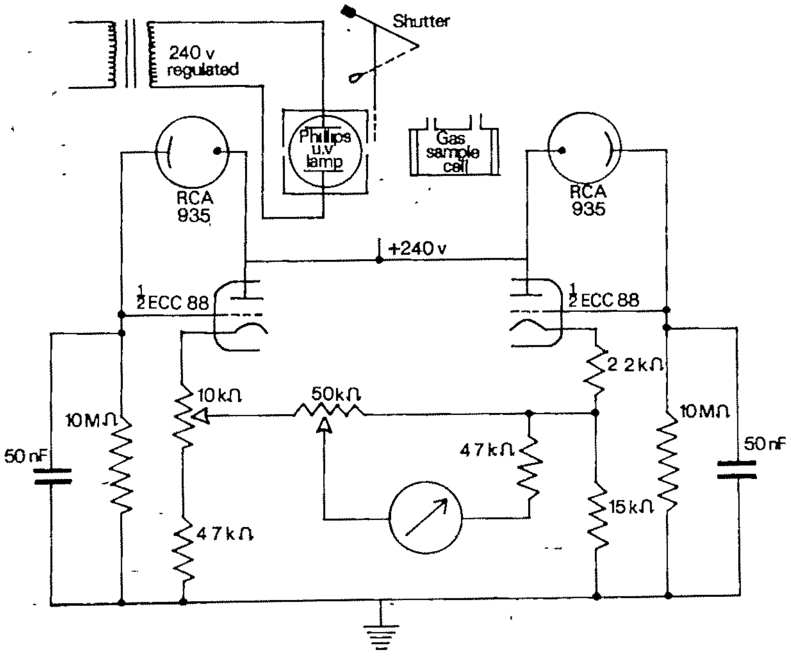

FIG. 1. Hook and Tucker design.

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0007–0912/80/111155–06 $01.00

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warmed up. The constant-voltage transformer was, however, effective in controlling any change in sensitivity after 15 min of use, provided the ambient temperature remained constant. On the other hand the zero reading could never stabilize, was liable to change erratically even after hours of use (fig. 5) and could drift by the whole span of the scale. This instability of the zero resulted from movement of the glowing plasma in the mercury lamp which altered the proportions of light falling on the two phototubes.

DESIGN

Design with beam splitter

In our first attempt to decrease this instability the phototubes were mounted side-by-side so that each had almost the same "view" of the lamp, but this resulted in only a limited improvement in performance. Therefore, we devised a new instrument in which a beam splitter was used to ensure that each phototube had an identical view of the lamp. This removed a large part of the zero drift, but left a small continuous drift as a result of a persistent differential fatigue of the two phototubes. Typically, this was of the order of halothane 0.3 vol % h^{-1}. Careful selection of pairs of phototubes was necessary to achieve this low rate of drift, although subsequent testing has shown that this fatigue appeared to be lessened even further with ageing of the phototubes. The general principles of this instrument are shown in figure 2.

The change in sensitivity because of lamp warm-up was eliminated by substituting an electronic control in place of the constant-voltage transformer. This control varied the power to the lamp to maintain a constant current in the reference phototube (the phototube not looking through the gas sample cell). In this way, a satisfactory instrument was produced using the same lamp and phototubes as the original.

Design with hot cathode lamp

Recently, a new design of mercury lamp has become available. This lamp (Cathodeon U-V lamp, type number HG1) has a hot cathode and this provides a more localized source of ultraviolet light as well as requiring a conveniently low voltage and current (16 V, 0.3 A). Using this lamp, it proved possible to achieve a stable distribution of light between two phototubes arranged side-by-side without the need to use a beam splitter.

To reduce the angle between the beams as much as possible, the cell diameter has been reduced from 22 mm in the Hook and Tucker instrument

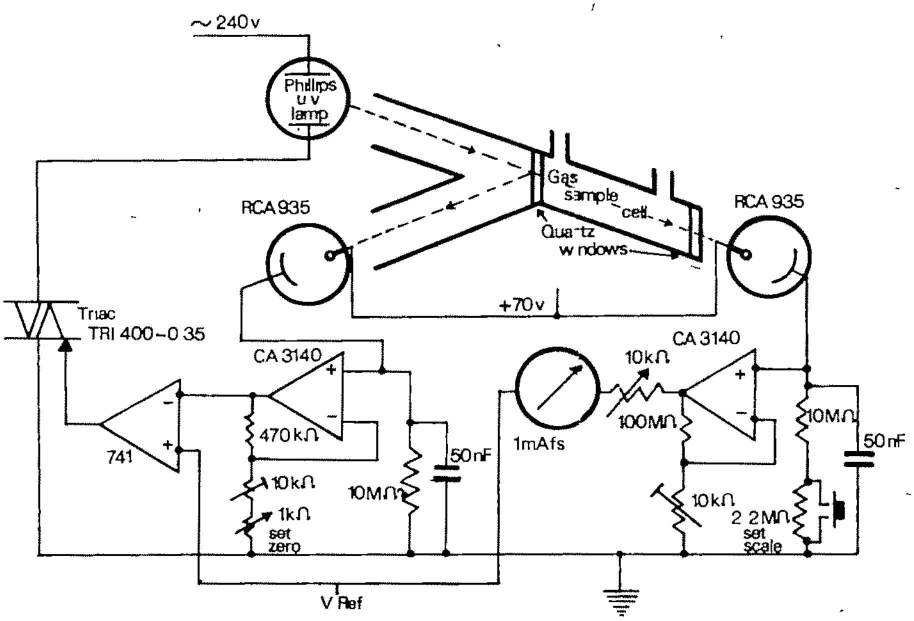

FIG. 2. Design with beam splitter

to a tube tapering, in steps, from 6 mm down to 3 mm and the length has been increased to 45 mm. This decrease in diameter is helpful in that it decreases the volume of gas required. The smaller aperture of the optical system means that the photocurrents are diminished significantly, from about 1 μA in the original to 10 nA in the current design. Such measurement is possible using modern operational amplifiers with insulated-gate field-effect transistors. The general principles of this instrument are shown in figure 3.

Further improvement in zero stability has been made possible by the use of new miniature phototubes (Hamamatsu R765). Unlike the RCA-type phototube used previously, these are sensitive to ultra-violet light only and have little sensitivity in the visible spectrum. This results in a greater percentage change in photocurrent for a given concentration of halothane.

As in the design with the beam splitter, compensation for the change in output of lamp light during warm-up is achieved by electrical feedback from the reference phototube.

It is interesting to note that, during our search for photodetectors better than the RCA 935 tubes, we tested the relative stability of several semiconductor photodiodes (both silicon and gallium arsenide) and found them much inferior to the Hamamatsu phototubes chosen finally. Only a small proportion of the overall response of the semi-conductors arose from those wavelengths absorbed by halothane. Tatnall, West and Morris (1978) overcame this disadvantage of semiconductor performance by using narrow-band filters.

PERFORMANCE

The new instrument with the hot cathode lamp has been tested against a Rayleigh refractometer and the resulting calibration curve is shown in figure 4. The voltage displayed in this figure is the meter voltage, which is exteriorized to the front panel via a buffer amplifier. The points shown represent the means of 12 readings on a digital voltmeter during a series of experiments. The standard error of each reading is estimated to be 5 mV; this represents less than halothane 0.03%. The full scale range of the instrument is designed to be 0–5%.

It is clear that the voltage is a non-linear function of halothane concentration, and we show in the Appendix that this function can be reproduced accurately by assuming that two spectral lines of the mercury light are involved, one of which is absorbed about 35 times more strongly than the other by passage through halothane.

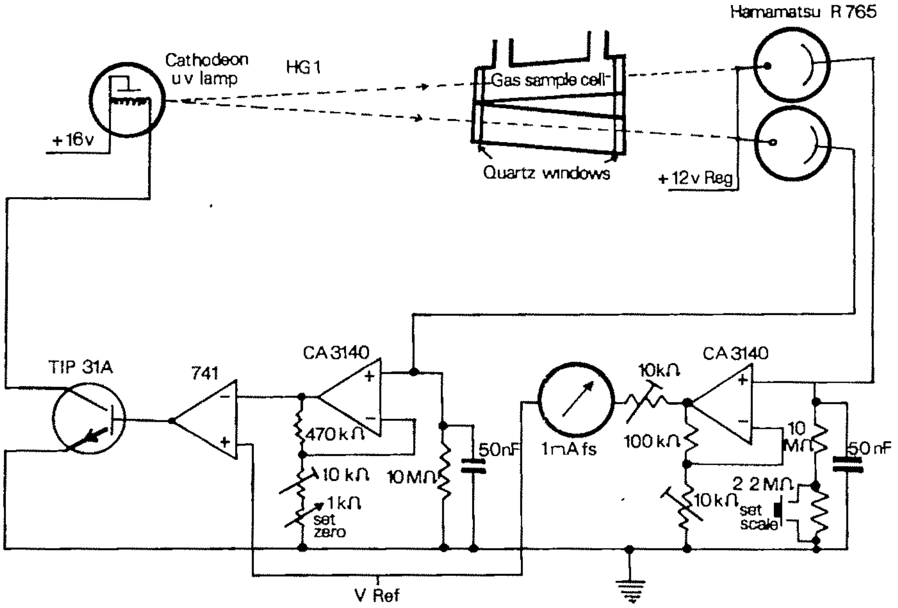

FIG. 3. Design with hot cathode lamp.

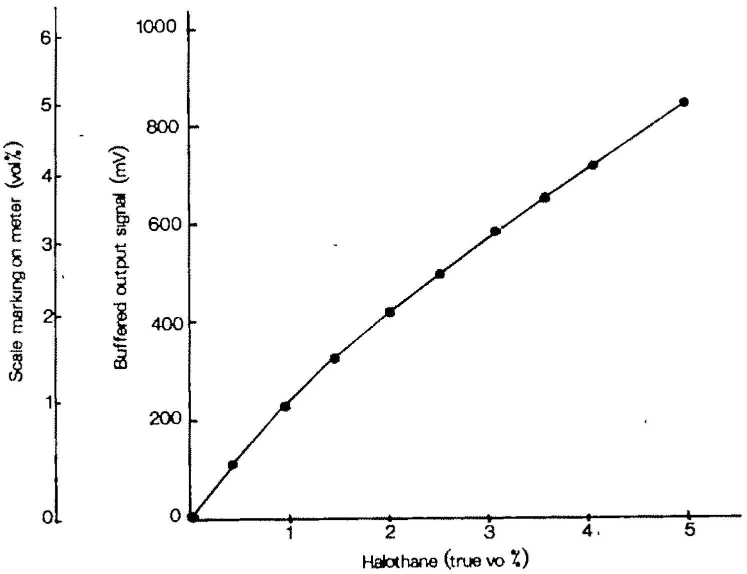

FIG. 4. Calibration curve for hot cathode lamp design.

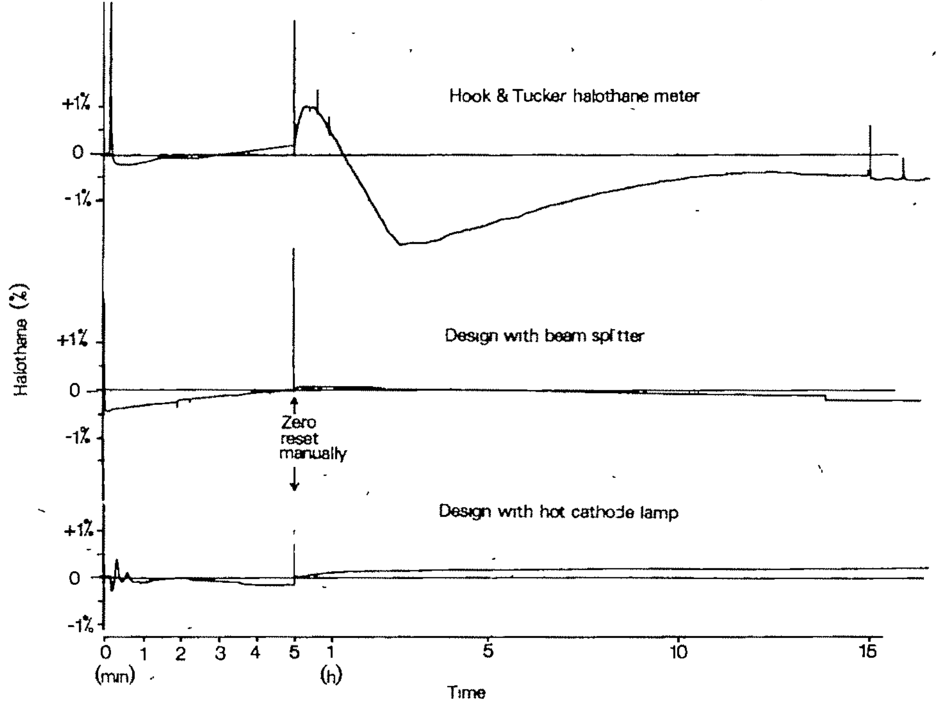

FIG. 5. Typical zero drift recordings of the three designs.

The non-linearity of the calibration will result in the meter scale being more open at the lower end than at the top, as can be seen from the scale drawn at the left hand side of figure 4.

Since this type of absorption meter measures the absolute concentration of halothane within the sample cell, its calibration in terms of volume per cent halothane implies standard atmospheric temperature and pressure and when used under any other conditions the scale will be somewhat in error. For practical purposes this effect is slight.

The volume of the sample cell is approximately 0.7 ml and with the sampling pump adjusted to its normal flow rate of 50 ml min^{-1} the 90% washout time is 1.5 s. The time-constant of the electrical circuits is less than 0.5 s. However, for practical purposes the dominant time delay is likely to be the transit time in the connecting tubing unless small-bore tubing is used. For example, the transit time for 2-mm bore tubing would be 4 s m^{-1} length.

To check the zero stability we have left the instrument running for 15 h. The instrument was set at zero and then allowed to stand with power off for at least 12 h. After 5 min use the zero was reset and then left untouched for the remainder of the test. A typical result, with comparable tests on the earlier instruments, are shown in figure 5.

The instruments with the hot cathode lamp is being developed commercially by Messrs Penlon Ltd. A prototype is shown in figure 6.

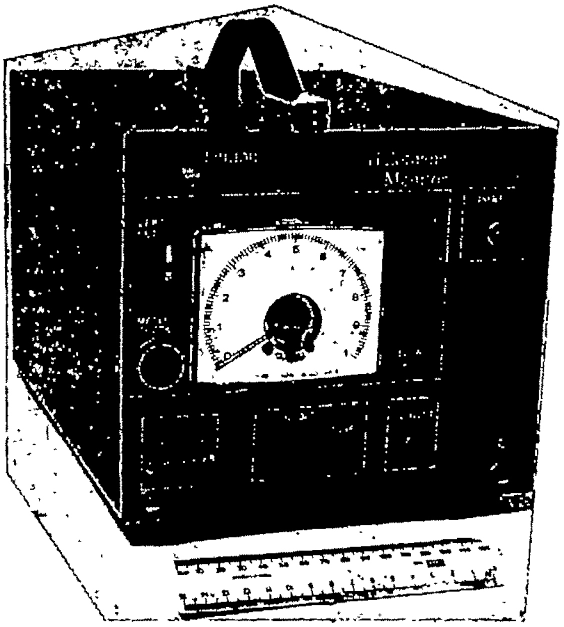

FIG. 6. The Penlon prototype.

APPENDIX

Beer's Law states that, for monochromatic light passing through an absorbing medium, the intensity is reduced according to the formula·

$$I = I_0 \exp(-bcx)$$

where I and I_0 are the intensities of the light before and after passing through the gas sample cell, b = the absorbency of halothane at the appropriate wavelength, c = the length of the cell, x = the density of halothane present (vol%)

If bcx is much less than 1.0, Beer's Law is equivalent to

$$I_0 - I = I_0\, bcx$$

It is clear from inspection of figure 4 that a single exponential will not fit the observed points, but that two exponentials might well do so. By sketching the two components in by freehand, we estimated them to be, approximately·

$$V_1 = 150\,(1 - \exp(-x))$$

and

$$V_2 = 5000\,(1 - \exp(-0.03x))$$

where V_1 and V_2 are the two components of the output (mV) Using a computer to optimize the fit to the observed data we ultimately arrived at the formula:

$$V_e = 129.7\,(1 - \exp(-1.1x)) + 4860\,(1 - \exp(-0.032x))$$

where V_e represents the total meter output (mV).

TABLE I. *Agreement between calculated* (V_e) *and observed* (V) *values of voltage*

Halothane (vol%)	V (mV)	V_e (mV)
0.4	110	108
0.95	230	230
1.43	320	320
2.00	417	417
2.50	494	495
3.06	578	579
3.54	648	648
4.05	719	719
5.00	848	848

Table I shows the agreement between the calculated and observed values of voltage V_e and V

These results confirm that the assumption of two spectral lines is adequate to explain the shape of the calibration curve.

ACKNOWLEDGEMENTS

This work has been supported by grants from the Wessex Regional Research Committee and the Scientific and Technical Branch of the Department of Health and Social Security. We wish also to thank Miss A. Maggs for her secretarial assistance

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APPAREIL DE MESURE DE L'HALOTHANE PAR ULTRAVIOLETS AMELIORE

RESUME

On donne une description de l'élaboration d'un appareil de mesure à absorption par ultraviolets qui permet d'évaluer les concentrations d'halothane (0–5%) dans des conditions cliniques. L'exactitude de l'échelle correspond à 0,05% et la déviation du zéro ne dépasse pas 0,25% d'halothane dans un délai de 15 h après une période de démarrage de 5 min. Le délai inhérent de réponse est d'environ 2 s.

EIN VERBESSERTER ULTRAVIOLETT-HALOTHANMESSER

ZUSAMMENFASSUNG

Die Entwicklung eines Ultraviolett-Absorptionsmessers, der sich für Messungen von Halothankonzentrationen (0–5%) unter klinischen Bedingungen eignet, wird beschrieben. Die Skala ist auf 0.05% genau und die Nullpunktwanderung ging nach einer Anwärmzeit von 5 Minuten über Zeitraum von 15 Stunden nicht über 0.25% Halothan hinaus. Die eigentliche Ansprechzeit beträgt ca. 2 Sekunden.

UN MEDIDOR DE HALOTANO POR ULTRAVIOLETA MEJORADO

SUMARIO

Se describe la elaboración de un medidor de absorción por ultravioleta apto para medir las concentraciones de halotano (0–5%) bajo condiciones clínicas. La escala es exacta al 0,05% y el desplazamiento del cero no excedió de un 0,25% de halotano durante 15 h después de un período de calentamiento de 5 min. El tiempo de respuesta inherente es de alrededor de 2 s.

Br. J. Anaesth. (1980), 52, 1161

FAIL-SAFE DEVICE FOR AN OXYGEN FAILURE IN ANAESTHETIC APPARATUS

K. A. FLOWER, N. H. NAQVI AND D. J. WOODS

SUMMARY

The criteria for an oxygen fail-safe device are designed to prevent a hypoxic gas mixture being administered to the patient should the oxygen supply fail, be disconnected, or be turned off. A fail-safe device which fulfils these criteria is described

Unfortunate accidents in operating theatres and casualty departments have occurred in which the oxygen supply to the anaesthetized patient has failed. In some instances patients have died and in others they have suffered permanent brain damage (Report, 1975).

Rosen and Hillard (1971) recommended that a complete fail-safe oxygen alarm system for anaesthetic apparatus should be based on the following seven features:

(1) It should be operated by the oxygen supply alone.
(2) When it is activated:
  (a) All gas and vapours from the anaesthetic apparatus to the patient should be stopped.
  (b) The breathing system should be open to the atmosphere.
  (c) Irrespective of the breathing system in use:
    (i) the inspired concentration of oxygen should be not less than that concentration found in air;
    (ii) there should be no increase in the concentration of carbon dioxide during either spontaneous breathing or artificial ventilation.
  (d) It should be impossible to begin the administration of an anaesthetic unless the initial oxygen supply is of an adequate pressure or unless such a supply is restored after a failure.
  (e) There should be a warning of impending oxygen supply failure.
  (f) There should be a further warning that failure has occurred.

Although several attempts have been made to produce a "fail-safe" device (Falkner Hill, 1956; Adler and Burn, 1967; Cooke and Waine, 1967; Lucas and Fisher, 1967; Ward, 1968; Rosen and Hillard, 1971) incidents in which patients are exposed to hypoxic gas occur still (Report, 1975). The majority of warning devices used currently depend either on the nitrous oxide supply for activation, or use the diminishing oxygen supply itself to sound an alarm. These devices are relatively satisfactory, but further improvement is required.

APPARATUS AND PROCEDURE

We have developed a fail-safe warning system powered by a low-voltage electrical supply. This system is based on two main components: the control valve (fig. 1) and the distribution valve (fig. 2).

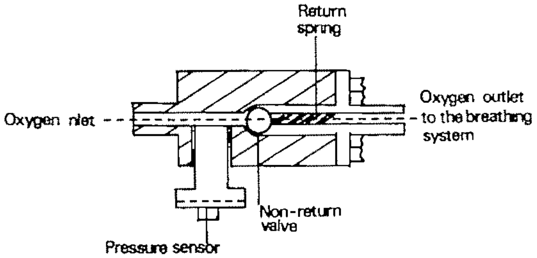

FIG. 1 The control valve

The control valve is placed in the system (fig. 3) in such a position that the oxygen supply to the breathing system is monitored continuously by

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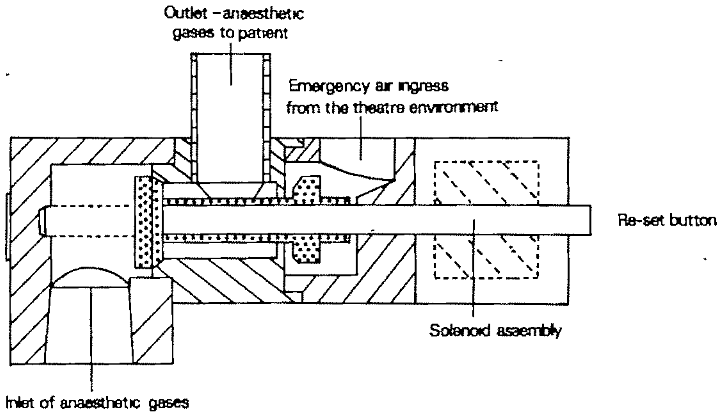
Outlet - anaesthetic gases to patient
Emergency air ingress from the theatre environment
Re-set button
Solenoid assembly
Inlet of anaesthetic gases

FIG 2. The distribution valve.

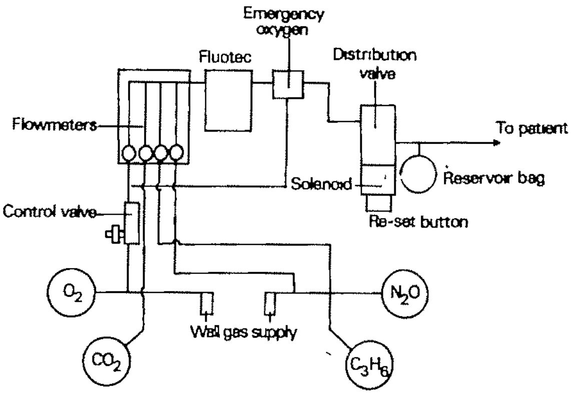

FIG. 3. Diagrammatic sketch of the breathing system.

this device. The entire breathing system only becomes functional and operational when the correct oxygen line pressure is established and maintained. This fulfils the principle described in item (d) above.

The sensitivity of the control valve may be preset to detect a decreasing variation in pressure of 3.448×10^4 Pa in any normal fixed pressure supply. Once the correct oxygen pressure has been detected by the control valve, the solenoid in the distribution valve allows the anaesthetic gases to be delivered to the patient.

In the event of an impending failure in the oxygen supply, the slight decrease in the oxygen pressure causes the following sequence:

(a) an alarm buzzer sounds;
(b) a warning light is illuminated;
(c) the patient is connected immediately to the theatre atmosphere;
(d) the anaesthetic vapour and gases are contained within the system and not vented to the theatre environment;
(e) the anaesthetic vapour and gases are isolated from the breathing system.

A special one-way valve (fig. 1) incorporated in the control valve ensures that the pressure sensor is not reactivated by the build-up of a back pressure caused by the containment of the anaesthetic gases and vapours within the circuit.

Re-establishment of the oxygen line pressure and the pressing of the distribution valve "reset" button cancel the alarms and allow the anaesthetic gases and vapours to enter the breathing system. The components of the control electrical circuit are shown in figure 4. These are encapsulated in a spark-proof epoxy resin and the recommended source of power is a small 12-V d.c. power pack.

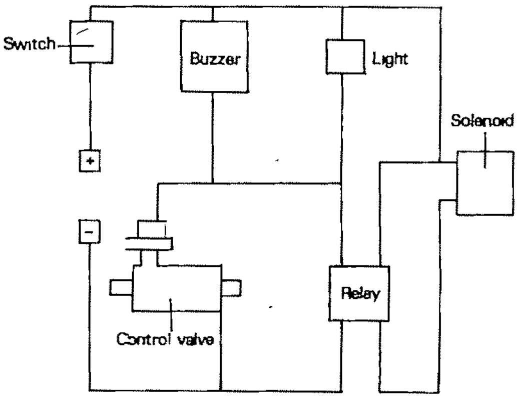

FIG. 4. Electrical control circuit.

Alternatively, a rechargeable 12-V battery may be used.

CONCLUSION

This fail-safe system can be fitted to any existing anaesthetic apparatus whether it utilizes cylinder gases or a central gas supply. The audible and visual warning of impending oxygen failure is continuous and will continue until the correct oxygen line pressure is restored. The oxygen valve is very sensitive to decreases in pressure and there is rapid response to any oxygen failure. The mode of operation of the pressure switch in the control valve is itself fail-safe. A failure of this unit would render the system inoperable. The encapsulation in a spark proof unit ensures complete safety and protection from any spark hazard. The device fulfils six of the seven principles laid down by Rosen and Hillard (1971). The seventh condition that the warning system should be based on a gas supply only, is felt to be outdated in 1980, as discussed in the introdution.

Further detailed specifications for this device are available from Dr K. A. Flower, The Aeronautical and Mechanical Engineering Department, University of Salford, Salford M5 4WT. Enquires regarding the manufacture of this device should be made to Dr Flower.

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DISPOSITIF DE SECURITE D'UN APPAREIL D'ANESTHESIE EN CAS DE MANQUE D'OXYGENE

RESUME

Les critères auxquels répond un mécanisme de sécurité contre manque d'oxygen sont conçus de façon à empêcher qu'un mélange de gaz hypoxique soit administré au malade, au cas où l'approvisionnement en oxygène vienne à manquer, à être débranché ou à être coupé. On donne la description d'un dispositif de sécurité qui répond à ces critères.

SICHERHEITSVORRICHTUNG FÜR SAUERSTOFFAUSFALL BEI NARKOSEGERÄTEN

ZUSAMMENFASSUNG

Die für eine Sauerstoff-Sicherheitsvorrichtung aufgestellten Kriterien zielen darauf hin, die Inhalation einer sauerstoffarmen Gasmischung durch den Patienten zu vermeiden, falls die Sauerstoffzufuhr versagen oder abgetrennt oder abgedreht werden sollte. Eine Sicherheitsvorrichtung, die diese Kriterien erfullt, wird beschrieben.

MECANISMO DE SEGURIDAD CONTRA LA FALTA DE OXIGENO EN UN APARATO DE ANESTESIA

SUMARIO

Los criterios en que se basa un mecanismo de seguridad del oxígeno tienden a impedir la administración al paciente de una mezcla de gas hipóxico, en caso de que la provisión de oxígeno falle, se desconecte o sea cortada. Se describe un mecanismo de seguridad que responde a dichos criterios.

Br. J. Anaesth. (1980), 52, 1165

BOOK REVIEWS

General Anaesthesia, 4th edn, Vol. 1. Edited by T. C. Gray, J. F. Nunn and J. E. Utting. Published by Butterworths. Pp. 905+appendices 17; illustrated; indexed. Price £40.00.

A new edition of this classic two-volume work on anaesthesia is always welcome, for it provides an assessment of the state of anaesthetic practice and an examination of how we have changed in the past decade. This edition has a new editor, Professor Utting, and, sadly, will be the last involving his predecessor at Liverpool, Professor Gray.

The first volume looks at the basis of anaesthetic practice, but not only in the sense of the current requirements for primary examinations of the Faculties of anaesthesia. Much is highly relevant to the final examinations. There are five sections, covering the fundamentals of anaesthetic action, the principles of conduction anaesthesia, the respiratory system, the cardiovascular system and the renal, hepatic, endocrine and other systems. The addition of the section on conduction anaesthesia is most welcome, for the days when it played only a minor role in British anaesthesia have gone for ever.

Each section is built up by a series of detailed reviews of the relevant topics by experts drawn largely, but not exclusively, from the United Kingdom. Their authority is evident and the readers will find each chapter to give a clear, comprehensive review of the current thinking on its topic. Perhaps the only criticism is that by reviewing so many topics (46 in this volume) the compression needed in dealing with each topic precludes a detailed consideration of the evidence on which the view has been reached. Nevertheless anyone wishing to update his knowledge on specific problems will find these chapters excellent starting places, for they add references with which the reader can expand his understanding.

Occasionally a statement appears which will pick up the reader sharply. For example, Dr Raftery believes that the most important single factor in the reduction of surgical mortality and morbidity in the past 50 years has been the recognition that correct and careful preparation of the patient is essential (p. 685). So much for the improved nutritional state and the reduction in chronic sepsis, let alone the introduction of blood transfusion, neuromuscular blockade, better monitoring, intensive care and the critical use of oxygen therapy, most of which are described in this edition. However, such statements are valuable and Dr Raftery goes on to give an excellent account of the preoperative assessment of the cardiovascular system.

This first volume will be used by anaesthetists at all stages of their careers. It is an excellent source book for candidates for examinations. Their seniors will find much helpful advice in the chapters on chronic exposure to trace concentrations of anaesthetics (Chapter 9), on oxygen toxicity (Chapter 28), on problems with the liver (Chapter 40) and with many other aspects of anaesthesia which have come into prominence in the past decade.

The book is superbly produced and will be a welcome and necessary addition to all anaesthetic libraries. It appears to be expensive, but its contents will repay the investment.

John Norman

General Anaesthesia, 4th edn, Vol. 2. Edited by T. C Gray, J. F. Nunn and J. E. Utting. Published by Butterworths, London. Pp. 881; illustrated, indexed. Price £40.00.

When I was first approached to review this book, the editor of the journal suggested that I should restrict myself to volume 2 and that he would find another reviewer for volume 1. At the time that seemed an excellent idea; the assessment of nearly 2000 pages of text is a fairly formidable undertaking and I was only too pleased to agree to the work being shared. Now, in retrospect, that was a great mistake; in past editions each volume had well-defined limits within which it was possible to treat it as a single book. However, it soon became clear that with this new edition both volumes were so interdependent that they had to be treated as one entity. Thus it is just not possible to do full justice to a text only half of which is available.

To some extent, of course, it depends on the reviewer's approach to his task, which will vary from one assessor to another. For myself, I prefer to read through the material to gain a general impression and thereafter to use it as a desk tool to check relevant information. This proved to be a frustrating exercise because almost invariably reference to the index indicated that the information sought was to be found in the first volume!

How, then, can one tackle the problem of reviewing such a text? In my view the simplest and perhaps the safest way is to invite the potential purchaser to check certain aspects for himself. The overall impression, the general layout, the character of the print, the value of the diagrams and the quality and usefulness of the photographs all help to build a picture which may or may not appeal to the potential reader. On the whole this volume earns good marks on these criteria, although one page in my book looked like a rather poor photocopy and some of the photographs were not particularly helpful.

Chapter headings are useful in that they indicate not only the subjects covered but also the editors' ideas of the order of importance and logical sequence. In this case many readers will find the editors' arrangements rather strange.

The next step is to consider the bibliographies. Where the reference list is short it is worthwhile looking at the dates of the entries. For example, if the latest reference quoted goes back to 1974 in a 1980 textbook (see p. 1485) or even 1971 (see p. 1218) the reader is entitled to ask how up to date the text is. Too many references can be just as much a handicap as too few, and it pays to check some at random to assesss their relevance. Some references can be singularly useless, particularly the personal communication (see p. 914) on a matter which can be no more than an expression of opinion, although even that might be justified if the authority cited was a Nobel prizewinner or a holder of the Order of Merit!

Most anaesthetists have certain fields of interest and therefore they can use their expert knowledge to check the validity of the information presented to them. For this volume I chose to consider five topics with which I could claim to be reasonably familiar; these were apnoeic diffusion oxygenation, cardiac dysrhythmias, closed circle anaesthesia, controlled hypotension and neuromuscular blocking drugs. It was gratifying to find that all five subjects were suitably indexed, although in the case of the dysrhythmias the word itself was not indexed, instead the old-fashioned "arrhythmia" was preferred

As far as basic information was concerned, the position was less satisfactory. Most people will accept that the introduction of apnoeic diffusion oxygenation into clinical practice resulted from the work of Martin Holmdahl in Uppsala and the late Lothar Barth in Berlin, neither of whom is mentioned in the text, although later references are given. Again, on the subject of cardiac dysrhythmias, it was claimed rightly (p. 916) that they could be produced by i.v. atropine and a 1963 reference was quoted in evidence, but there must be many references going back at least 50 years which make the same point I can certainly name several without much difficulty. Clearly, arguments about priority of discovery can be distasteful, but there can be little justification for quoting the first reference that comes to mind. That form of mental idleness is an insult to the reader and a reflection on the authors.

On the topic of closed circle anaesthesia, I was not too enlightened and I certainly take objection to the suggestion in the classification of methods of administration that the difference between semi-open and semi-closed techniques is a matter of semantics. That is not true, but the statement may reflect the fact that the authors concerned probably have never used a semi-open technique. The essential difference between open and closed techniques, however qualified, is that the patient's oxygen supply is derived from the atmosphere with an open method, whereas it comes from a cylinder with a closed technique. Typically a semi-open technique is used for the administration of ether by a Schimmelbusch mask. It is made semi-open by wrapping a towel round the head and mask to ensure that the concentration of ether is maintained; this produces a substantial degree of re-breathing.

When controlled hypotension is considered the claim (p 1149) that the first deliberate reduction of arterial pressure in surgery was by Griffiths and Gillies in 1948 is not correct. Some years earlier (1943) W. J. Gardner described the use of controlled hypotension by deliberate arterial bleeding in the management of anaesthesia for neurosurgery and while the technique may no longer have any great clinical relevance, it was a major advance at the time, and those of us who were deeply involved with the so-called surgical trespass of that decade will not readily forget the lessons to be learned from Gardner's revolutionary approach and from the experimental work that led to it.

According to the index, most of the information about neuromuscular block and about the drugs used for this purpose is contained in the first volume Certainly the anaesthetist in trouble with these drugs would not find too much helpful advice in the volume under review, but perhaps it has all been said elsewhere. It is to be hoped so.

Despite the overall comprehensive approach which the editors obviously required of their contributors, there is a marked absence of historical perspective and the text is not strengthened by a shortage of the detailed information necessary to handle the types of problem that frequently present during anaesthetic practice.

In summary, some good reading and some excellent bibliography make this a useful volume, but—value for money? I wonder.

J. P. Payne

Anesthesia for Obstetrics. Edited by S. M. Shnider and G. Levinson. Published by Williams & Wilkins, Baltimore and London. Pp. 456; illustrated; indexed. Price £12.50.

This is a new textbook with contributions from the editors and 17 other authors—all but one of them from North America. It covers all aspects of obstetric anaesthesia and its aim is to provide an up-to-date review as a sound basis for the safe practice of anaesthesia in obstetrics.

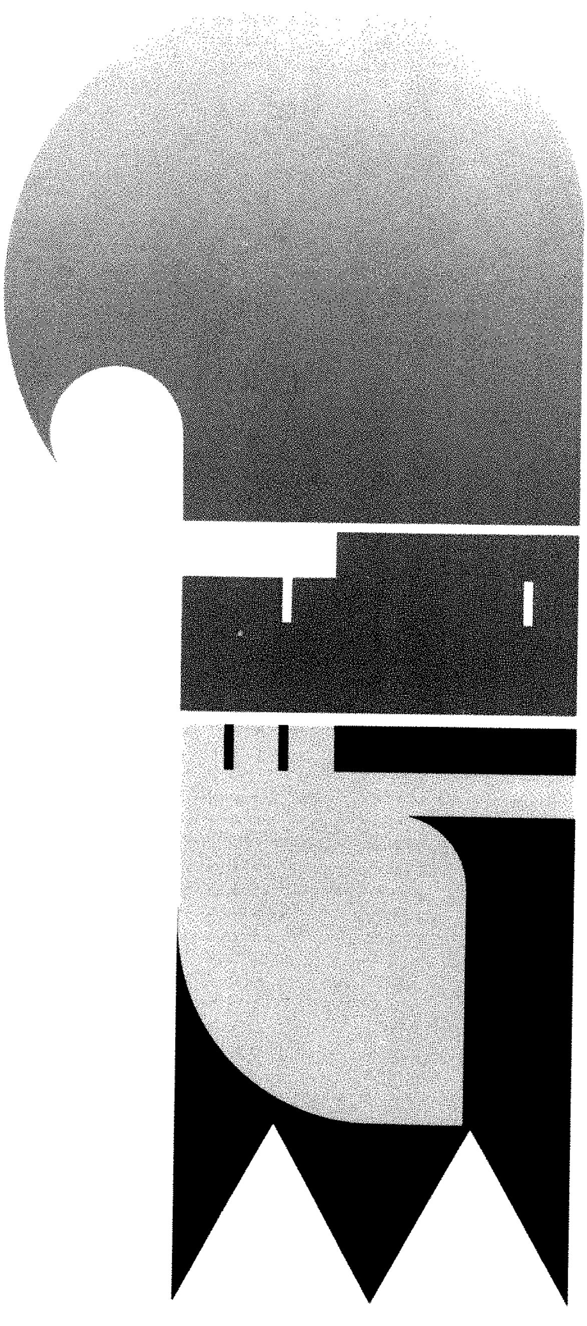
The contents are divided into sections on obstetric physiology and pharmacology, anaesthesia for vaginal delivery, complicated obstetrics, anaesthetic complications and the fetus and newborn. In addition there are appendices containing a table of the fetal effects of maternally administered drugs and the anaesthetic and paediatric charts used in the University of California.

This textbook is orientated towards North American practice and because of this some drugs in use in Europe are not discussed, but in every other way this is an excellent book which is informative, well referenced, readable and easy to consult. In particular, the chapter on perinatal pharmacology is well done with very clear illustrations of an often confusing concept of placental transfer of drugs. The section on anaesthesia for vaginal delivery is comprehensive to the extent of devoting 10 pages to psychological anaesthesia for obstetrics (some illumination is required at least to read the section on the LeBoyer technique). Another laudable feature is the description of the pharmacology and adverse effects of drugs prescribed by the obstetrician during labour, for example β-adrenergic agents for pre-term labour. A sign of the times, in the U.S.A. at least, is the inclusion of a chapter on lawsuits in obstetric anaesthesia. Lastly, the section on evaluation and care of the newborn is invaluable.

There are two criticisms. The first is that at times the authors have attempted to be too authoritarian and comprehensive and many controversies appear in this text as fact. Presenting unheard of side-effects of drugs supported by one case report is an example of this. Second, the book is very American and makes little attempt to be anything else American references are favoured and European key references ignored. When will American authors accept that it may be worth attempting to mention drugs which are in common use in other parts of the world?

In spite of these criticisms, this book is recommended to everyone concerned with the care of a woman during childbirth as well as being a worthwhile read before F.F.A.R.C S.

Walter S. Nimmo



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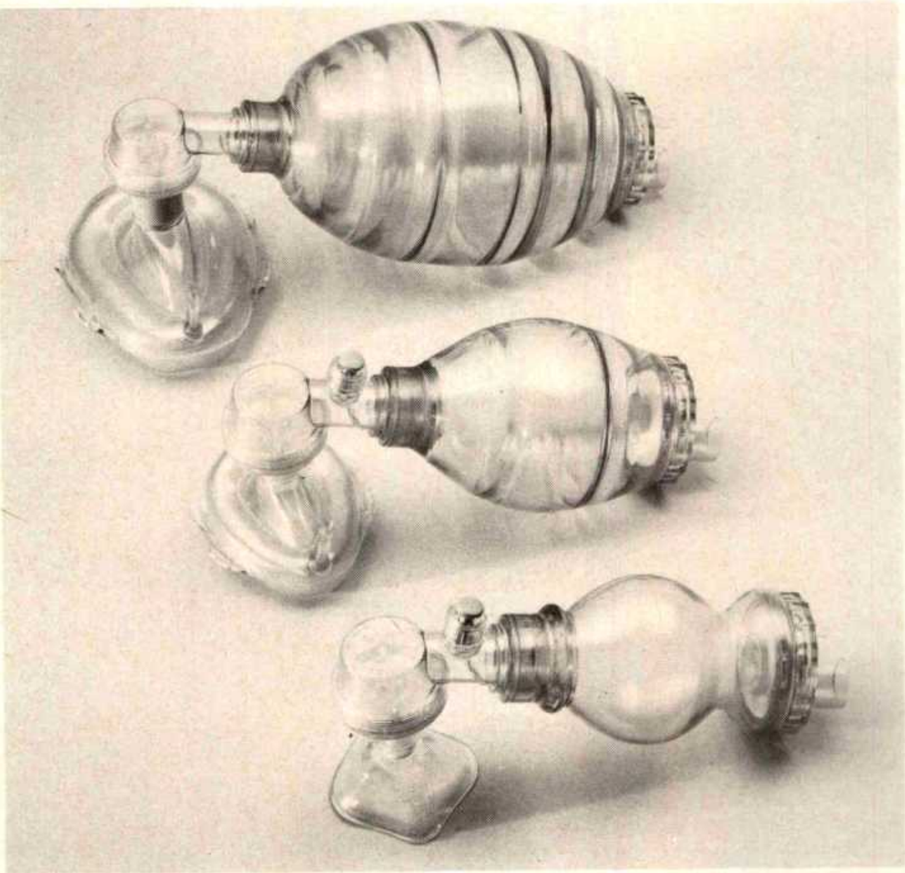

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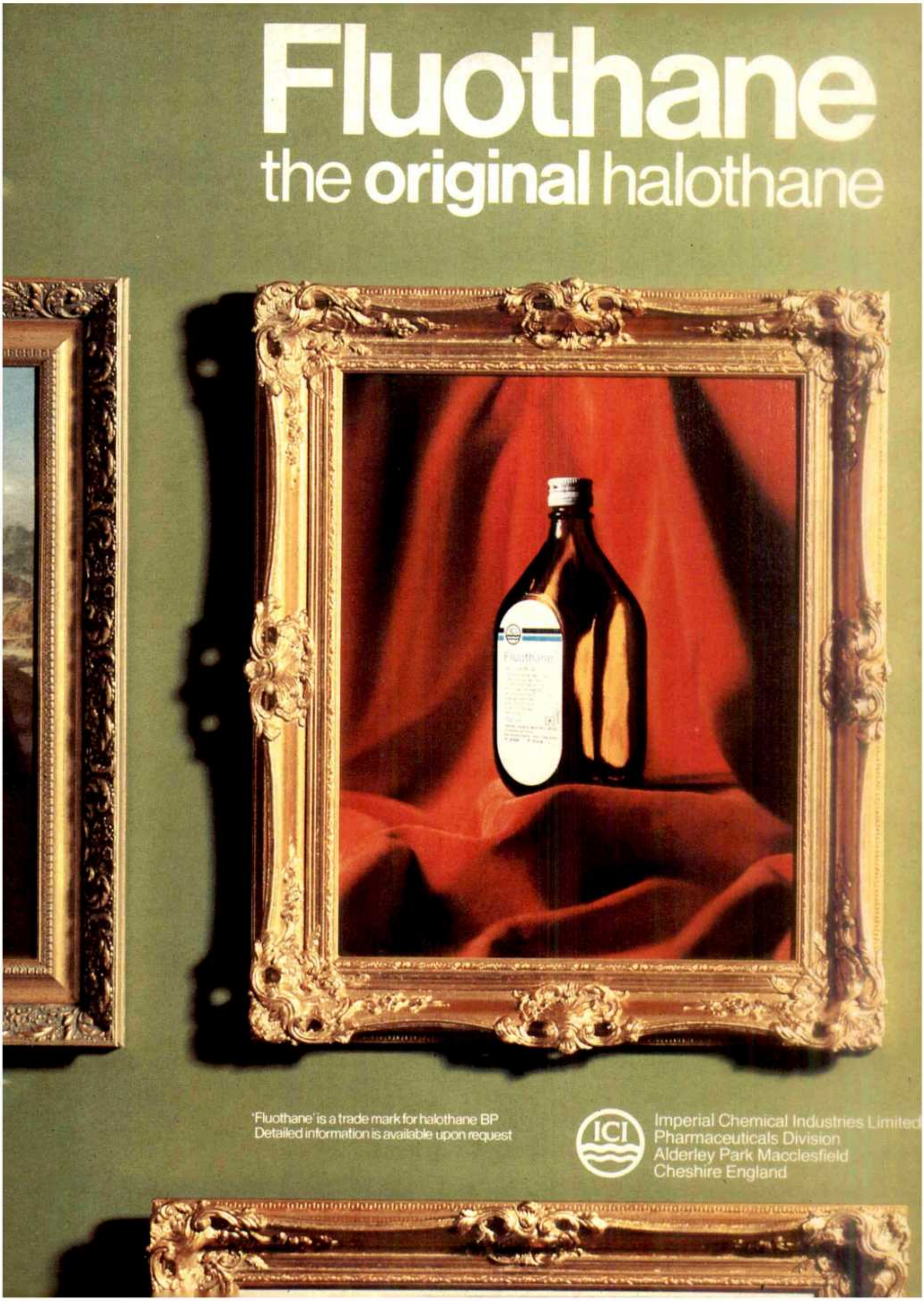

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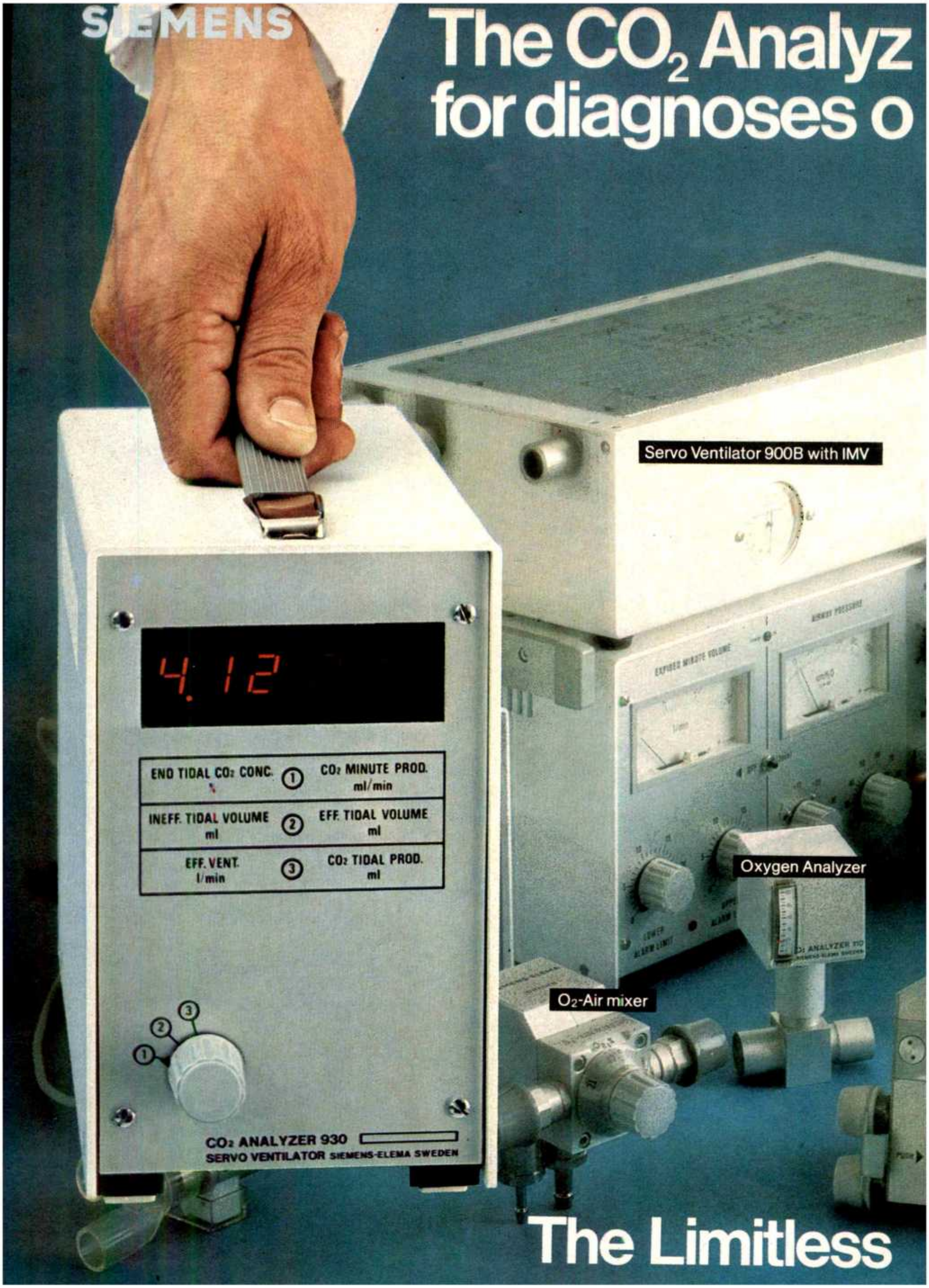
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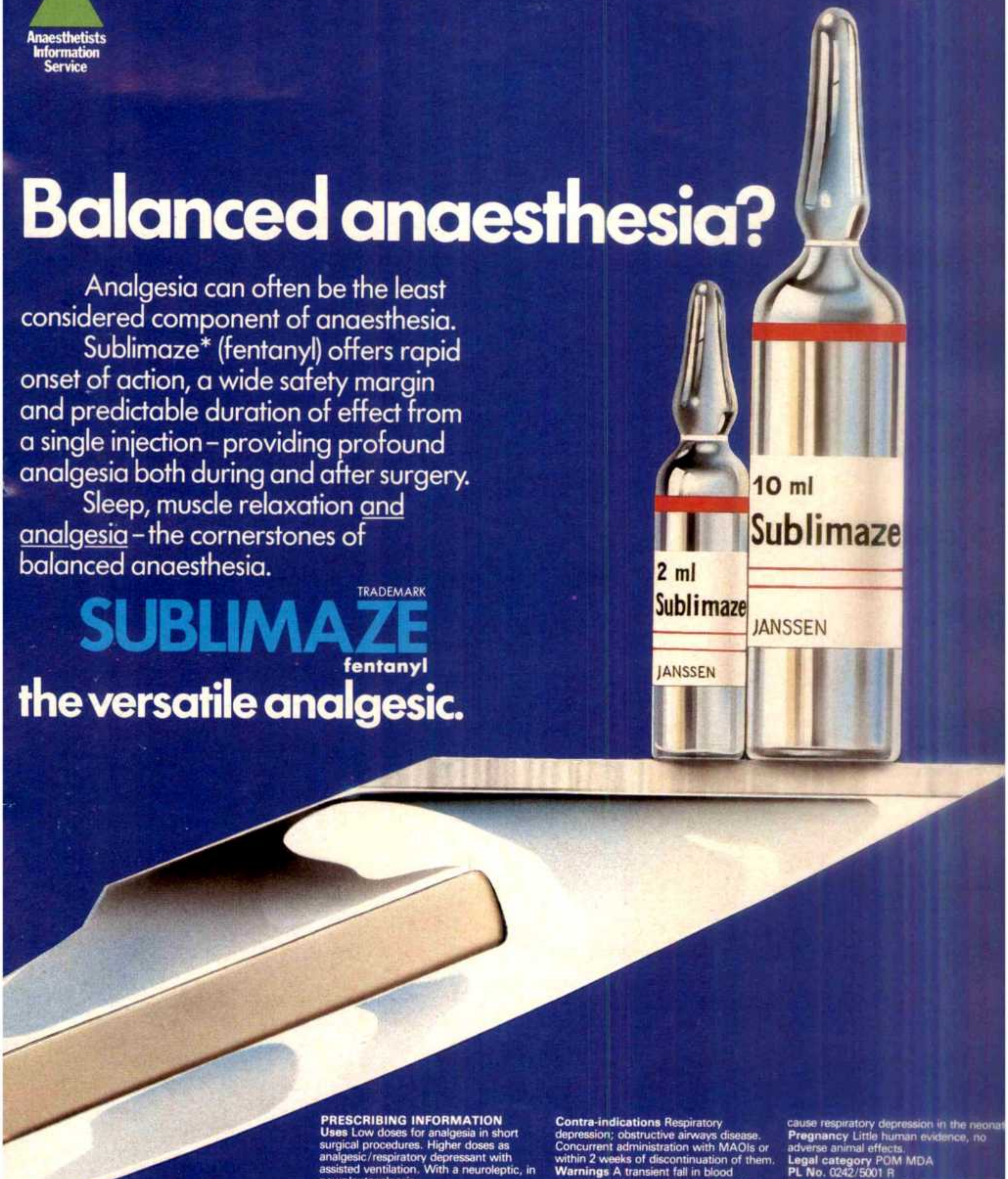

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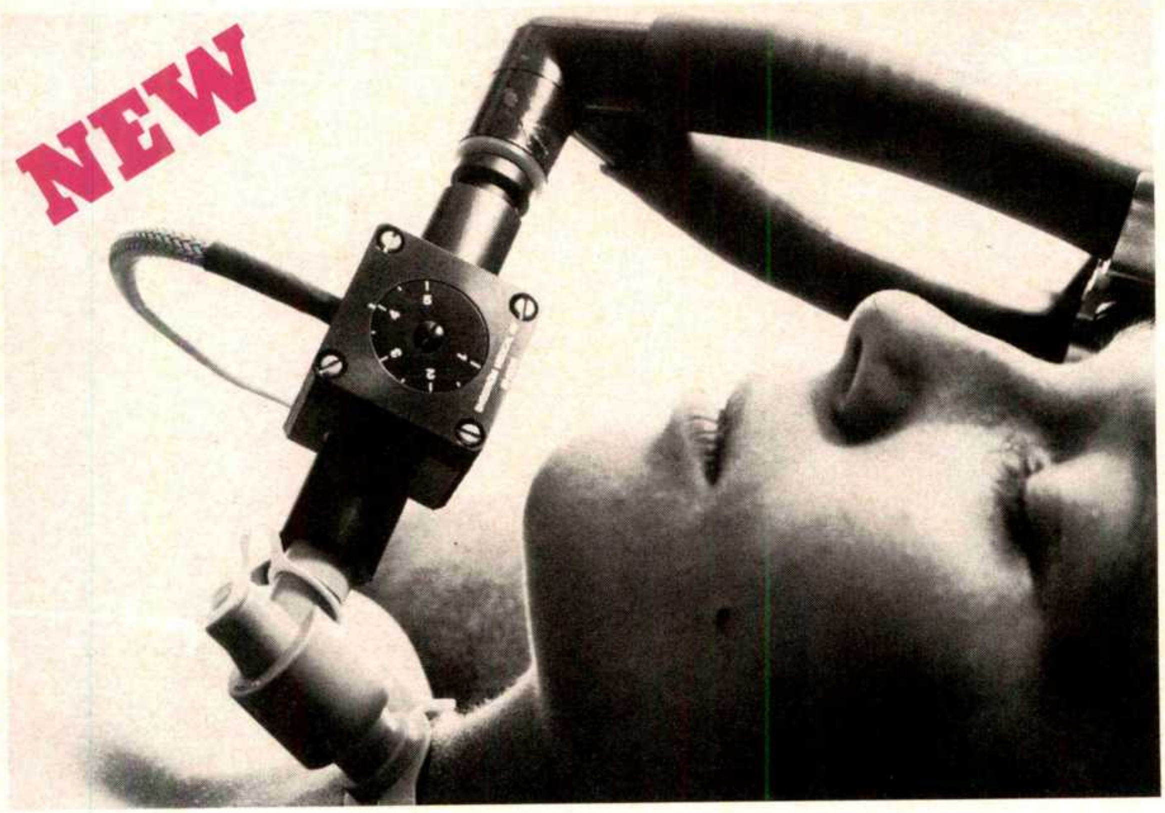

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VOLUME 52, No. 12 DECEMBER 1980

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EDITORIAL

THE INTENSITY AND DURATION OF ACTION OF I.V. DRUGS

In using drugs given as i.v. bolus injections, anaesthetists would like to know how much effect is likely to be produced, how long that effect will last and what factors may alter either the intensity or duration of effect. Now that it is becoming easier to measure the plasma concentrations of many drugs and, occasionally as with the neuromuscular blocking drugs, some of their effects, investigators are reporting results which should give the answers to these questions. The mathematical modelling and analysis needed appear complex and Feldman (1980) has criticized this science of pharmacokinetics and pharmacodynamics as being the "pop-art of anaesthesia". The variety of ways of presenting pharmacokinetic data and the increasing complexity of one-, two- three- and effector-compartment modelling seems to substantiate his claim. Nevertheless, there are some possibilities of arriving at conclusions from such studies which will help the clinical anaesthetist.

Pharmacokinetic analysis is concerned with the uptake, distribution and elimination of drugs in the body (Greenblatt and Koch-Weser, 1975a, b; Hull, 1979a). Essentially, it deals with what the body does to the drug. For many of the drugs used as i.v. bolus injections the following will give the essential characteristics of the processes involved: the *distribution* and *elimination half-lives*, the *volume* of the *central compartment* and the *volume of distribution* and the *clearance* of the drugs. If a two-compartment model can be fitted to the plasma drug concentration curve, then these parameters and the dose of drug used allow calculations of all the other constants. More important it may be possible to attach some significance to the terms.

The distribution and elimination half-lives characterize the rates at which the drug is initially distributed by the circulation to the tissues of the body (the first, faster process) and the rate at which the drug is eliminated. Of course, some elimination occurs in the distribution phase and redistribution occurs in the elimination phase, but as an initial concept the two can be separated. Distribution half-lives are usually short and of the order of a few minutes. Elimination half-lives may be long as they reflect the processes of elimination by metabolism of the drug or renal excretion, or both; they may be influenced by hepatic and renal disease. The central compartment volume reflects the initial dilution of the drug and the volume of distribution the overall dilution of drug in the body. Concern may be felt that a volume, especially a volume of distribution, may be larger in capacity than the body mass, but if it is remembered that volumes are calculated from plasma concentrations and doses of drugs given, and that drugs are often bound to body proteins or are more soluble in lipids than water, then the concern may disappear. Both these processes reduce the drug concentration in plasma and increase the apparent volumes. Halothane would be expected to have a large volume of distribution.

The clearance of a drug is useful in obtaining some idea of the overall rate at which drug will be removed, but it should be considered with the volume of distribution. If that is large then a very high clearance may be needed if the drug is to be removed rapidly from the body.

From these ideas it is now possible to calculate the plasma concentration at any given time and also the concentration of drug in the mythical second compartment (Wagner, 1975). What is being done now is to relate these concentrations to the effects produced. With neuromuscular blocking drugs some progress has been made, but there are problems. During recovery from the effects of an i.v. bolus there is a good correlation between plasma concentration and effect, but this is not so during the onset of paralysis, for whilst the plasma concentration is declining the paralysis is increasing. It might be thought that the paralysis might match the calculated concentrations in the second compartment, but several groups of workers have found this is not so (Hull et al., 1978; Shanks, Somogy and Triggs, 1979; Sheiner et al., 1979). To overcome this problem these authors are adding to the two-compartment model a third, small, effector compartment. By suitably juggling (with the aid of a computer) the measured effects with the postulated parameters of the third compartment they are able to come up with ideas as to how the intensity and duration of effects will be determined.

The computer modelling produces the concentrations of drug in the small effector compartment which follow the same time course as the degree of relaxation. Thus, at 50% paralysis the concentration should be the same during both onset and recovery from a neuromuscular blocking drug. To some extent this must assume that the rates at which the drugs bind to and are released from the receptors are much faster than the processes of bringing drug to and removing it from the effector zone. Once these effector concentrations are worked out it is possible to analyse the dose–response curve to determine what concentrations produce what percentage effect and a measure of the slope of the dose–response curve. There is a variety of transformations possible to give a linear fit of the relationship between concentration and effect. Norman (1979) described some of them.

In this issue Drs Hull, English and Sibbald use this type of analysis to compare the actions of fazadinium and pancuronium. The usefulness of these models is in making predictions as to how long a given dose will produce paralysis and what will be the effect of subsequent doses. The final test of their usefulness will come subsequently in seeing if the models work.

The general reader is going to have some trouble in comparing results from one set of workers with another. Some problems arise with the symbols used. It is to be hoped that Hull's proposed standard set (Hull, 1979b) will reduce the confusion. Some arises because, although only one drug may be being studied, the assay techniques are not the same. Readers should look for the sensitivity of the tests and whether the assay detects unchanged drug or includes metabolites and whether the effects of plasma protein binding are considered. Some problems are associated with the duration of the blood-sampling. Studies limited to 2 or 3 hours may well give different results to those of 8 or 24 hours. One precaution necessary with neuromuscular blocking drugs is that a simple fitting of measured paralysis against drug concentration in whatever transformation used will not necessarily convey how the antagonist is combining with the receptors; there are just too many steps between acetylcholine release and the production of a muscle contraction for this to have much meaning.

There is one final problem. Studies such as those of Hull, English and Sibbald (1980) are time consuming, expensive and often may be performed only in a few subjects. Statistical evaluation of the results often presents the averages together with some idea of the weighting to be put on that average (usually the standard error of the mean). Perhaps in the future, for those of us dealing with individual patients, it would be better to give some idea of the dispersion of results using standard deviation or tolerance limits. Then, perhaps, we can use these results to forecast what will happen when we use drugs, new or old, in varying doses in varying patients. The pop-art would then become popular.

John Norman

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TIME OF DEATH OF AN ORGAN DONOR

"*To many an average chap, there is nothing like complete and prolonged cessation of the circulation as the hall mark of final and irrecoverable death*" (Evans, Stein and Lum, 1980). This quotation was paraphrased by the mother of an 18-year old kidney donor in a public letter (Moore, 1980) in which she stated further, "*I then had the ultimate agony . . . of having to walk away . . . while he was still pink and warm, and breathing, albeit on a ventilator . . . . I tried to tell myself (he) was indeed dead, and even insisted upon seeing him after the kidneys had been removed . . . he then looked quite awful . . . . I needed to see that (he) had stopped breathing . . . . I shall always wonder about his death.*"

These sentiments are commonly experienced by close relatives of organ donors, and the non-acceptance of *brain death* as a final event should be recognized as a normal reaction to this tragic situation. Yet there is little if any comment on this in the recent Code of Practice drawn up by a Working Party of the Departments of Health entitled *The removal of cadaveric organs for tranplantation.*

Brain death is a recent concept which has become necessary, first, to justify withdrawing life support systems such as ventilation of the lungs, and second, to enable organs for donation to be removed in good condition from a "cadaver". "Brain death" was granted legal acceptance when the Bradford and Calderdale Coroner, Mr Turnbull, accepted this diagnosis in an inquest on a 20-year-old female on February 22, 1978.

The implications of the diagnosis of brain death must be fully appreciated. It is still common to find recorded the time of cessation of heart beat. This is irrelevant. Somatic life continues for hours—or even days in the case of hair follicles—after the heart beat ceases. A clear distinction should be made between brain death and somatic death and the certified time of death should be the time the final brain death diagnosis is made.

It is helpful if a patient's relatives are informed of the way in which the diagnosis is made, and that usually a clear plan is followed (for example the recommendations of the Medical Royal Colleges reported in the *British Medical Journal* (1976), 4, 1187). One major advantage of this would be for the relatives to understand that the patient is unable to breathe, and that ventilation and breathing are not the same.

When organ transplantation is envisaged, it is important for the relatives to know that the staff involved in the primary care of the patient are not the same as those who will be involved in the transplant surgery. Difficulty arises when a member of the primary care team broaches the question of transplantation to the next of kin. If, after this, the patient's somatic life is prolonged for the convenience of the transplant team, it is hardly surprising the next of kin wonder about their relative's death.

It will be some time before "brain death" is accepted as a final event, particularly when the patient's general condition may have remained unchanged for several hours. Relatives may be helped by a considerate explanation of the circumstances, which in turn depends on the medical profession's acceptance of "brain death" as death.

F. R. Ellis

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ACKNOWLEDGEMENT

The Editor wishes to acknowledge the help of the following who, in addition to the Editorial Board, provided help with the assessment of manuscripts during 1980.

Professor A. P. Adams
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Br. J. Anaesth. (1980), 52, 1171

PHYSOSTIGMINE ANTAGONIZES MORPHINE-INDUCED RESPIRATORY DEPRESSION BUT NOT ANALGESIA IN DOGS AND RABBITS

M. WEINSTOCK, D. ROLL, E. EREZ AND M. BAHAR

SUMMARY

The ability of physostigmine to antagonize the respiratory depressant effect of morphine was studied in conscious rabbits and ketamine-anaesthetized dogs pretreated with atropine methyl nitrate. Morphine 4 mg kg^{-1} increased Pa_{CO_2} in the rabbit from 3.43 ± 0.16 to 4.95 ± 0.28 kPa, decreased arterial pH from 7.45 ± 0.01 to 7.31 ± 0.01 and decreased respiratory frequency by 36%. Physostigmine 0.1 mg kg^{-1} reduced Pa_{CO_2} to control values within 10 min and significantly increased arterial pH and respiratory frequency. There was no antagonism of the analgesic effect of morphine. Neostigmine 0.1 mg kg^{-1} did not reverse the respiratory depressant effect of morphine. In dogs anaesthetized with ketamine, morphine 15 mg kg^{-1} caused loss of consciousness and marked analgesia, decreased the respiratory frequency by 47%, and increased Pa_{CO_2} by 47%. Physostigmine 0.1 mg kg^{-1} antagonized the effect of morphine on respiration and restored consciousness in the dogs, but did not impair analgesia. It is concluded that physostigmine reverses morphine-induced respiratory depression by prolonging the effect of acetylcholine released from brain-stem neurones. The possibility should be considered of replacing opiate antagonists by physostigmine to reverse postoperative respiratory depression and drowsiness induced by opiates.

Physostigmine salicylate is an anticholinesterase which, unlike the commonly used agent neostigmine, is a tertiary amine, and therefore readily penetrates the blood–brain barrier. In decerebrate cats pretreated with physostigmine, application of acetylcholine (Ach) to the floor of the 4th ventricle markedly stimulates breathing (Miller, 1949).

Morphine and related narcotic analgesic drugs are known to produce respiratory depression by decreasing the sensitivity of the respiratory centre to carbon dioxide (Jaffe and Martin, 1975). The site of the respiratory depressant action of morphine has been localized to the lower brain stem (Florez, McCarthy and Borison, 1968). A number of studies in different species have demonstrated that opiates can inhibit the release of Ach from neurones in the central and peripheral nervous system (Jhamandas, Phillis and Pinsky, 1971; Weinstock, 1971; Domino and Wilson, 1973; Zsilla et al., 1977). It is possible that opiates depress respiration by reducing the availability of Ach in the vicinity of the respiratory centre (Schaumann, 1958). If this was so, it would be likely that physostigmine could reverse the respiratory depressant effect of morphine by preventing the hydrolysis of Ach. Since physostigmine itself (Flodmark and Wramner, 1945) and directly-acting cholinergic agonists such as oxotremorine and pilocarpine, have been shown to produce analgesia in animals and man (Ireson, 1970; Dayton and Garrett, 1973), it was considered unlikely that physostigmine would interfere with the analgesic activity of morphine.

MATERIALS AND METHODS

Male New Zealand rabbits, weight 2.5–3.0 kg, were trained to sit quietly in a restraining box. Blood samples (0.5 ml) for gas analysis were taken through a catheter (Quick Cath. 20 gauge Travenol Labs, Ireland Ltd) placed in the ear artery and filled with sterile saline containing heparin 25 u. ml^{-1}. Drugs were administered through a 19 gauge butterfly needle placed in a marginal ear vein.

Rectal temperature was monitored with a telethermometer (Yellow Springs Instruments) from a thermistor probe inserted to the rectum. Respiratory frequency was counted visually and blood-gas tensions and pH measured with a Corning automatic blood-gas analyser after correction for the appropriate body temperature.

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0007-0912/80/121171-06 $01.00

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Analgesia was assessed from the reaction (squeal or attempt at withdrawal) in response to one of four grades of pressure applied to the tip of the tail with a sponge holder clamp. A score of 1 indicated a positive reaction to the lowest grade of pressure, while 5 denoted that no reaction occurred to the highest grade of pressure.

Rabbits were allowed to rest for 1 h after cannulation before control readings were taken. Drugs were not given until two consistent values for blood-gas tensions were obtained. All rabbits were pretreated with atropine methyl nitrate (ATMN) 1 mg kg^{-1}. In six rabbits, morphine 4 mg kg^{-1} was injected slowly i.v. over a period of 2–3 min. Respiratory frequency was counted and blood samples for gas analysis were collected at 30, 60 and 90 min after injection of morphine. In 12 other rabbits, physostigmine 0.1 mg kg^{-1} or neostigmine 0.1 mg kg^{-1} was injected i.v. immediately after the 30-min blood sample had been collected following morphine administration. Further blood samples for gas analysis were collected at 5, 10, 20, 30 and 60 min after physostigmine. At the end of the experiment, rabbits were returned to their cages.

Ketamine anaesthetized dogs

Five mongrel dogs of either sex, weight 10–13 kg, were used. Animals were re-used after an interval of 10 days. The dogs were anaesthetized with ketamine 20 mg kg^{-1} i.m. This agent was used in preference to a barbiturate, since these are known to inhibit strongly cholinergic neurones in the c.n.s. (Bradley and Dray, 1973; Weinstock et al., 1979). Furthermore, ketamine itself does not significantly depress respiration at anaesthetic doses (Waterman and Livingston, 1978). The femoral artery was cannulated ("Venflon" Viggo 18 gauge) under aseptic conditions. The cannula was filled with sterile saline containing heparin 50 u. ml^{-1}. The brachial vein was also cannulated and sterile dextrose 5% was perfused continuously through the catheter at the rate of 2 ml min^{-1}.

A rectal thermistor probe was inserted and body temperature monitored continuously with a Yellow Springs telethermometer. ATMN 0.5 mg kg^{-1} was injected i.v. Ten minutes later (30 min after induction of anaesthesia), respiratory frequency was counted and arterial blood samples were taken for the measurement of blood-gas tensions and pH.

Morphine was then administered by i.v. infusion at the rate of 0.3 mg kg min^{-1}. Analgesia was assessed at 10-min intervals on a 1–5 scale as described in rabbits, by the reaction to pressure applied to the ear. Respiration rate, blood-gas tensions and pH were measured every 15 min.

We determined the dose of morphine which:

(a) prevented the animal from responding to sound or other external stimuli;

(b) increased the analgesic score to at least 4;

(c) reduced the respiratory frequency by at least 40%;

(d) increased Pa_{CO_2} by 40%;

(e) maintained the above levels of analgesia and respiratory depression for at least 60 min after cessation of the morphine infusion.

Physostigmine 0.1 mg kg^{-1} was injected i.v. 60 min after the end of the infusion of morphine. Analgesia, respiratory frequency and blood-gas tensions were measured 15 and 30 min later. At the end of the experiment, cannulae were removed and the animal allowed to recover consciousness before returning to the animal house. Solutions of physostigmine were made up in sterile saline containing absorbic acid 1 mg ml^{-1} and sterilized by filtration before use.

RESULTS

Conscious rabbits

The mean control respiratory frequency of 18 conscious rabbits was 110±8 b.p.m., mean Pa_{CO_2} 3.43±0.16 kPa and mean pH 7.45±0.01. These values are within the normal range for rabbits. Body temperature was 38.9±1.2 °C (Altman and Dittner, 1971).

I.v. injection of morphine 4 mg kg^{-1} markedly reduced respiratory frequency in the rabbits, peak depression occurring between 30 and 60 min after i.v. injection (table I). Maximum reductions in blood pH and Pa_{O_2} and increases in Pa_{CO_2} also occurred at this time (fig. 1). Good analgesia was obtained at 30 and 60 min after morphine as indicated by mean scores in six rabbits of 4.56±0.22 and 4.50±0.21, respectively, out of a total possible score of 5.0.

Injection of physostigmine 0.1 ml kg^{-1} significantly increased respiratory frequency and blood pH, slightly increased Pa_{O_2} and decreased Pa_{CO_2} to control values, within 5–10 min. The reversal of the respiratory depressant effects of morphine by physostigmine lasted at least 60 min (fig. 1 and table I). There was no reduction in the level of analgesia induced by morphine following the in-

TABLE I. *The effect of physostigmine and neostigmine on respiratory frequency and analgesia induced by morphine in the rabbit.* *P < 0.05 *by paired* t *test compared with morphine alone;* **P < 0.01 *by paired* t *test compared with control alone*

Treatment	*n*	Time after morphine (min)	Time after physostigmine or neostigmine (min)	Respiratory frequency (b.p.m. ± SEM)	Analgesia scores (± SEM)
Control (before drug)	18	0	0	110±8	1.29±0.12
Morphine 4 mg kg^{-1}	6	30	0	69±9**	4.48±0.24**
		60	0	72±8	4.02±0.23
Morphine 4 mg kg^{-1} + physostigmine 0.1 mg kg^{-1}	6	35	5	98±10*	4.91±0.30
		40	10	77±10	4.80±0.28
		50	20	78±14	4.51±0.29
		60	30	80±12	4.12±0.27
Morphine 4 mg kg^{-1} + neostigmine 0.1 mg kg^{-1}	6	35	5	70±10	4.40±0.26
		50	20	68±9	4.21±0.27
		60	30	67±8	4.01±0.23

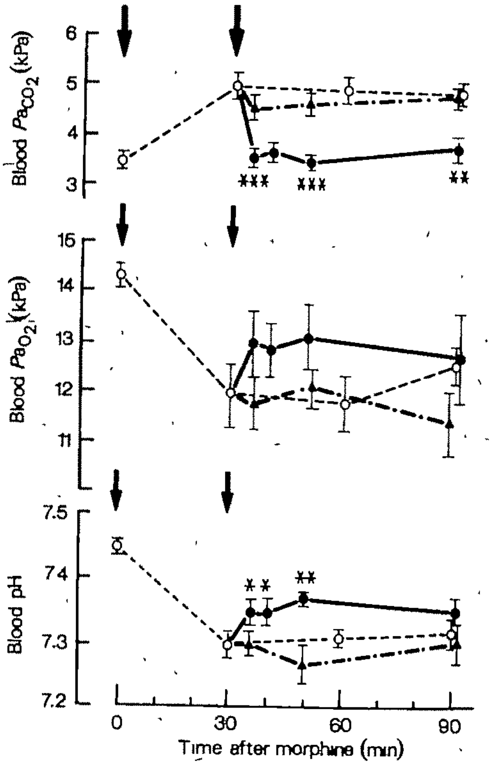

FIG. 1. Effect of physostigmine 0.1 mg (●——●) and neostigmine 0.1 mg (▲---▲) (right-hand arrows, 30 min) on changes in arterial blood gases and pH induced by morphine 4 mg kg^{-1} (○—○) (left-hand arrows, 0 min). Each point represents the mean value ± SEM from six rabbits. **$P < 0.01$; ***$P < 0.001$; compared with morphine alone by one-tailed test.

jection of physostigmine (table I). There were also no signs of peripheral cholinergic effects such as lachrymation, miosis, salivation, defaecation or micturition following physostigmine after pretreatment with ATMN 1 mg kg^{-1}. In one rabbit in which Pa_{CO_2} was increased from 3.33 to 6.52 kPa by morphine 8 mg kg^{-1}, physostigmine 0.1 mg kg^{-1} reduced Pa_{CO_2} to 4.52 kPa and a further dose of 0.1 mg kg^{-1}, given 10 min later, reduced Pa_{CO_2} to 3.46 kPa.

Neostigmine 0.1 mg kg^{-1} injected 30 min after morphine 4 mg kg^{-1}, to six other rabbits, did not significantly alter any of the respiratory variables depressed by morphine. Larger doses of neostigmine (0.2–0.3 mg kg^{-1}) caused marked fasciculations and increased the respiratory depressant effect of morphine.

Dogs anaesthetized with ketamine

Pretreatment of the dogs with ketamine prevented the usual manifestations of excitement, "sham rage", hyperventilation and howling, that normally occur when morphine is given i.v. to conscious dogs (preliminary findings in this laboratory, and Fennessy and Ortiz, 1968). The mean respiratory frequency in dogs before ketamine was 24±2. Thirty minutes after ketamine, it increased to 30±4. Results for blood-gas tensions, pH and analgesia after ketamine are shown in table II. The normal Pa_{CO_2} for unanaesthetized dogs is 5.05 kPa (Altman and Dittner, 1971).

A total of morphine 15 mg kg^{-1} was given to obtain the required increase in analgesia and respiratory depression. The effects produced 30–90 min after this dose of morphine are shown in table II.

TABLE II. *Effect of physostigmine on changes in respiratory frequency, arterial blood-gas tensions and analgesia induced by morphine in the dog. Values are mean ± SEM from five dogs given either morphine alone or morphine followed 60 min later by physostigmine. Compared with morphine alone, 60 min or 90 min.* $^{*}P<0.05$; $^{**}P<0.01$

Treatment	Time after morphine (min)	Respiratory frequency (b.p.m. ± SEM)	pH	Pa_{CO_2} (kPa ± SEM)	Pa_{O_2} (kPa ± SEM)	Analgesic score (± SEM)
Control (ketamine 20 mg kg^{-1} + ATMN 0.5 mg kg^{-1})	−20	30.0 ± 4.0	7.37 ± 0.03	4.55 ± 0.23	12.63 ± 0.53	2.0 ± 0.4
Morphine 15 mg kg^{-1}	30	16.0 ± 0.4	7.21 ± 0.04	6.60 ± 0.24	10.11 ± 0.27	4.3 ± 0.2
	60	15.5 ± 0.8	7.20 ± 0.04	6.69 ± 0.29	10.37 ± 0.27	4.2 ± 0.3
	90	16.5 ± 0.8	7.21 ± 0.03	6.44 ± 0.25	10.91 ± 0.27	3.5 ± 0.3
Morphine 15 mg + physostigmine 0.1 mg kg^{-1}	75	20.0 ± 0.9**	7.25 ± 0.02	5.21 ± 0.31**	10.91 ± 0.27*	4.8 ± 0.2
	90	18.0 ± 1.0	7.22 ± 0.02	5.85 ± 0.32	10.91 ± 0.40	3.7 ± 0.4

When physostigmine 0.1 mg kg^{-1} was given 60 min after the end of the morphine infusion, the dog sat up, looked around the room and responded to sounds within 10 min. After a further 5 min, there was a significant increase in both the rate and depth of respiration which was accompanied by an increase in pH and Pa_{O_2} and a decrease in Pa_{CO_2} (table II). However, there was no difference in the level of analgesia from that obtained before physostigmine was given, as indicated by the virtual absence of a response to pressure on the ear. Thirty minutes after physostigmine, the dogs became sedated once again, and the respiratory depressant effect of morphine also returned. In one of the dogs, a further injection of physostigmine 0.1 mg kg^{-1} restored respiratory frequency and Pa_{CO_2} to pre-morphine values.

DISCUSSION

Central cholinergic mechanisms have often been implicated in various actions of morphine (Weinstock, 1971). While morphine has been shown to inhibit Ach release from neurones in the brain (Jhamandas, Phillis and Pinsky, 1971; Domino and Wilson, 1973), other studies have shown that the analgesic activity (Saxena, 1958), toxicity (Brister and Davis, 1974) and morphine withdrawal syndrome can be modified by drugs that stimulate or block cholinergic receptors (Jhamandas, Sutak and Bell, 1973).

Apart from an early study in rats anaesthetized with urethane (Schaumann, 1958), a detailed investigation of the action of anticholinesterases on the respiratory depressant action of opiates does not appear to have been carried out.

This study demonstrated that physostigmine can cause reversal of the respiratory depressant effect of morphine in conscious rabbits. Although physostigmine altered both the frequency of respiration and the blood Pa_{CO_2} significantly, more importance can be attached to the latter measurement, since we have observed that marked changes in spontaneous respiratory frequency can occur in conscious rabbits with little change in blood-gas tensions. The depth of respiration, which was seen to change but not measured, would doubtless explain alterations obtained in blood-gas tensions.

ATMN did not prevent the effect of physostigmine and morphine reversal was not achieved with neostigmine, which shows that central cholinergic neurones are involved in the interaction between morphine and physostigmine.

In dogs anaesthetized with ketamine and given large doses of morphine, physostigmine produced a prompt recovery of consciousness lasting at least 15 min without reducing analgesic activity. It is unlikely that the reversal of the narcosis by physostigmine resulted from antagonism of ketamine rather than morphine. Although physostigmine has been shown to reduce ketamine-induced sleeping time in rats (Lawrence and Livingston, 1979) and sedation in humans (Balmer and Wyte, 1977), an interval of at least 2 h had elapsed in the experiments between the injection of ketamine and that of physostigmine. In dogs, the duration of anaesthetic effect of ketamine 20 mg kg^{-1} alone was found to be only 20–30 min.

It is therefore reasonable to conclude that physostigmine can antagonize the hypnotic and respiratory depressant effects of morphine without impairing its analgesic activity.

We suggest that physostigmine be used in place of conventional narcotic antagonists for the reversal of postoperative respiratory depression induced by opiates. It may be possible to maintain the desired level of analgesia, while the patient remains fully awake and breathing normally, by suitably spaced injections or an infusion of physostigmine.

ACKNOWLEDGEMENTS

Supported by a VSPHS grant from NIDA, RO1 DA 02150-01 and by the joint Research Fund of the Hebrew University and Hadassah, and the Herbert Singer Funds for medical Research.

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LA PHYSOSTIGMINE CONTRARIE LA DEPRESSION RESPIRATOIRE DUE A LA MORPHINE, MAIS N'AFFECTE PAS L'ANALGESIE CHEZ LES CHIENS ET LES LAPINS

RESUME

On a procédé à l'étude de l'aptitude de la physostigmine de contrarier l'effet déprimant de la morphine sur la respiration chez des lapins ayant leur connaissance et des chiens anesthésiés à la kétamine, préalablement traités au nitrate de méthyle d'atropine. Chez le lapin, sous l'effet de 4 mg kg^{-1} de morphine. le Pa_{CO_2} augmenta de 3,43 ± 0,16 à 4,95 ± 0,28 kPa, le pH artériel baissa de 7,45 ± 0,01 à 7,31 ± 0,01 et la fréquence respiratoire descendit de 36%. La physostigmine, en dose de 0,1 mg kg^{-1}, eut pour effet de réduire en 10 min le Pa_{CO_2} aux valeurs de contrôle et d'accroître de manière significative le pH artériel et la fréquence respiratoire. Elle ne contraria pas l'effet analgésique de la morphine. La néostigmine en dose de 0,1 mg kg^{-1} ne contraria pas l'effet déprimant de la morphine sur la respiration. Chez des chiens anesthésiés à la kétamine, 15 mg kg^{-1} de morphine provoquèrent une perte de connaissance et une analgésie marquée, une diminution de 47% de la fréquence respiratoire et une augmentation de 47% du Pa_{CO_2}. La physostigmine, en dose de 0,1 mg kg^{-1}, contraria l'effet de la morphine sur la respiration et rendit la connaissance aux chiens, mais n'affecta pas contrairement l'analgésie. On en conclut que la physostigmine change le cours de la dépression respiratoire causée par la morphine en prolongeant l'effet de l'acétylcholine produite par les neurones du tronc cérébral. Il convient de tenir compte de la possibilité de remplacer les substances opiacées antagoniques par de la physostigmine afin de contrarier la dépression respiratoire postopératoire et la somnolence causées par les opiats.

PHYSOSTIGMINE BEKÄMPFT DIE MORPHIN-INDUZIERTE EINSCHRÄNKUNG DER ATMUNGSFUNKTION ABER NICHT DIE ANALGESIE BEI HUNDEN UND KANINCHEN

ZUSAMMENFASSUNG

Die Fähigkeit von Physostigmine, die atmungseinschränkende Wirkung von Morphin zu bekämpfen, wurde bei vollem Bewusstsein bei Kaninchen und bei ketaminanästhetisierten Hunden, die mit Atropinmethylnitrat vorbehandelt worden waren, studiert. Morphin 4 mg kg^{-1} verursachte eine Zunahme der Pa_{CO_2} beim Kaninchen von 3,43 ± 0,16 auf 4,95 ± 0,28 kPa, eine Abnahme des arteriellen pH Wertes von 7,45 ± 0,01 auf 7,31 ± 0,01 und eine Verringerung des Atmungsfrequenz um 36%. Physostigmine 0.1 mg kg^{-1} reduzierte Pa_{CO_2} auf Kontrollwerte innerhalb 10 Minuten und führte zu einer bedeutenden Zunahme des arteriellen pH-Wertes und der Atmungsfrequenz. Es fand keine Bekämpfung der analgesischen Wirkung von Morphin statt. Neostigmine 0,1 mg kg^{-1} hat die atmungseinschränkende Wirkung von Morphin nicht rückgängig gemacht. Bei Hunden, die mit Ketamine anästhetisiert waren, führte Morphin 15 mg kg^{-1} zu Bewusstseinsverlust und ausgeprägter Analgesie, einer Verminderung der Atmungsfrequenz um 47% und einer Zunahme der Pa_{CO_2} um 47%. Physostigmine 0,1 mg kg^{-1} bekämpfe die Wirkung von Morphin auf die Atmung und stellte das Bewusstsein der Hunde wieder her, beeinträchtigte die Analgesie aber in keiner Weise. Es wird geschlossen, dass Physostigmine die morphininduzierte Atmungseinschränkung rückgängig macht, indem es die Wirkung von Acetylcholine verlängert, die von den Hirnstammneuronen abgegeben wird. Man sollte die Möglichkeit erwägen, Opiatbekämpfungsmittel durch Physostigmine zu ersetzen, um die durch Opiate induzierte postoperative Atmungseinschränkung und Schläfrigkeit rückgängig zu machen.

LA FISOESTIGMINA ANTAGONIZA A LA DEPRESION RESPIRATORIA INDUCIDA POR LA MORFINA, PERO NO ASI A LA ANALGESIA EN PERROS Y CONEJOS

SUMARIO

La capacidad de la fisoestigmina para antagonizar el efecto deprimente de la morfina fue objeto de un estudio en conejos con conocimiento y en perros anestesiados por quetamina que habían recibido un pretratamiento por nitrato de metilo de atropina. En el conejo, 4 mg kg^{-1} de morfina tuvieron por efecto de aumentar el Pa_{CO_2} desde 3,43 ± 0,16 hasta 4,95 ± 0,28 kPa, de reducir el pH arterial desde 7,45 ± 0,01 hasta 7,31 ± 0,01 y de disminuir la frecuencia respiratoria en un 36%. Dentro de 10 min, 0,1 mg kg^{-1} de fisoestigmina hizo bajar el Pa_{CO_2} hasta los valores de control e incrementar de manera significativa el pH arterial y la frecuencia respiratoria. No hubo antagonismo al efecto analgésico de la morfina. No invirtió el efecto deprimente respiratorio de la morfina la administración de 0,1 mg kg^{-1} de neoestigmina. En perros anestesiados con quetamina, 15 mg kg^{-1} de morfina provocaron la pérdida de conocimiento y una analgesia marcada, redujeron la frecuencia respiratoria en un 47% y aumentaron el Pa_{CO_2} en un 47%. La fisoestigmina, en dosis de 0,1 mg kg^{-1}, antagonizó el efecto de la morfina sobre la respiración et hizo recobrar el conocimiento a los perros, pero no impidió la analgesia. Se llega a la conclusión de que la fisoestigmina invierte la depresión respiratoria inducida por la morfina al prolongar la acción de la acetilcolina liberada por los neurones del tronco cerebral. Ha de considerarse la posibilidad de reemplazar las substancias opiadas antagonizadoras por fisoestigmina con miras a invertir la depresión respiratoria postoperatoria y la modorra inducidas por los opiatos.

Br. J. Anaesth. (1980), 52, 1177

OXYGEN-LINKED BINDING OF HALOTHANE TO HUMAN ADULT HAEMOGLOBIN

P. GUESNON, B. BOHN, E. BURSAUX AND C. POYART

SUMMARY

The affinity for oxygen of normal adult human haemoglobin (Hb) solutions was measured in the presence of increasing concentrations of halothane. We observed a maximum increase in P_{50} of 25% with halothane 40 kPa compared with control (oxygen–argon gas mixtures) indicating the oxygen-linked character of the binding of halothane to the Hb molecule. The effect of halothane on P_{50} was independent of pH between 7.0 and 8.0 and of chloride concentration between 10 and 100 mmol litre^{-1}. This suggests that halothane–Hb interactions may occur through hydrophobic linkage as occurs with short chain aliphatic hydrocarbons. The oxygen-linked binding of halothane appears of minor importance in altering oxygen binding to Hb *in vivo* compared with other factors such as chloride ion or 2, 3-DPG.

The binding of halothane to human adult haemoglobin was demonstrated by different authors with various techniques (Schoenborn, 1968; Laasberg and Hedley-White, 1971; Barker et al., 1975). It was not known if binding was affected by oxygenation of Hb. If a difference existed between the binding constant of halothane to reduced and fully oxygenated Hb, a change would be predicted in the affinity of Hb for oxygen (Antonini and Brunori, 1971). The addition of halothane to whole blood was reported to induce a decrease (Gillies et al., 1970; Smith, Colton and Behar, 1970) or no effect (Millar, Beard and Hulands, 1971; Waltemath, 1971; Weiskopf, Nishimura and Severinghaus, 1971) on the affinity of Hb for oxygen. These discrepancies may be explained as technical error since halothane has been shown to alter the response of polarographic $P\text{O}_2$ electrodes used in some of these experiments (Dent and Netter, 1976; McHugh, Epstein and Longnecker, 1979) or from the large influence of various anion cofactors on the oxygen affinity of Hb in the erythrocytes which may make a small effect of halothane difficult to detect. It was demonstrated in this laboratory that short-chain aliphatic hydrocarbons such as pentane, pentene or butene decrease the oxygen affinity of purified Hb A solutions independent of pH and ionic strength of the buffer solutions (Poyart et al., 1979). This suggested that non-electrostatic interactions, probably hydrophobic, were responsible for the effect.

Halothane is chemically similar to these short-chain hydrocarbons and we investigated its effect on the affinity for oxygen of isolated normal adult Hb and on the alkaline Bohr effect.

METHODS

Experiments

Oxygen binding studies were carried out on purified, stripped HbA ($\alpha_2\,\beta_2$) solutions at a concentration of 10 g litre^{-1} at 25 °C. The preparation of HbA from whole normal adult blood has been described previously (Poyart, Bursaux and Bohn, 1978). The purity of the fraction used was checked by isoelectric focusing (Multiphor LKB, Bromma, Sweden) which displayed one single band. Aliquots of stock Hb solution were diluted in bis Tris HCl 50 mmol litre^{-1} or Tris HCl buffers containing sodium chloride. Four types of solution were prepared: two pH 7.0 and 8.0 containing sodium chloride 100 mmol litre^{-1} and two also pH 7.0 and 8.0 containing sodium chloride 10 mmol litre^{-1}. The four solutions allow rapid study of the effects of pH and anions on Hb.

The measurements of P_{50} were performed with a discontinuous equilibrium method (Poyart, Bursaux and Bohn, 1978). Two millilitre of diluted Hb solution was deoxygenated under humidified argon at 25 °C in a glass tonometer attached to an optical glass cuvette. The glass vessel was sealed during the experiment and had two ports.

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0007-0912/80/121177-05 $01 00

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One was sealed with a rubber cap to allow injection into the tonometer of a reagent or gas; the second port allowed gas to flow at constant pressure inside the vessel. Deoxygenation of Hb solutions usually lasted 10 min and was judged to be complete when the ratio of the absorbance at 554.5 nm to that at 540 nm was at least 1.25 (Van Assendelft, 1970). This ratio also indicates a negligible amount of methaemoglobin. After recording the spectrum of the deoxygenated Hb (Pye Unicam SP 1800 Spectrophotometer), small amounts (0.1–0.2 ml) of pure oxygen were introduced to the vessel through the rubber-capped side hole with a Hamilton syringe. The Hb solution was equilibrated at 25 °C for 7 min by gentle shaking and the same volume of gas was withdrawn to keep pressure inside the vessel constant. The spectrum of the partially oxygenated Hb was recorded and readings of absorbance made at 576.5 and 560 nm. Five or six points on the oxygen binding curve were determined for each experiment. Finally the spectrum of fully oxygenated Hb was obtained after equilibrating the solution with pure humidified oxygen. The amount of methaemoglobin formed during the experiments did not exceed 5%, estimated from the ratio A_{520}/A_{540} of fully oxygenated Hb.

Experiments with halothane were carried out with the same technique except that, after deoxygenation with argon, the vessel was filled with various concentrations of halothane in argon and equilibrated for 20 min at 25 °C. Argon saturated with halothane at 25 °C was obtained by bubbling argon 100 ml min^{-1} through halothane. Various concentrations of halothane were obtained by mixing flows of halothane-saturated argon with humidified argon using two precision flowmeters (Laboratoires Houdec, Corbeil, France). After the experiments with halothane, the spectra of fully oxygenated Hb were recorded with the same fraction of halothane but mixed with pure oxygen. No changes in deoxygenated or in fully oxygenated spectra (from 510 to 630 nm) were observed in the presence of halothane, which indicates that halothane did not produce any alteration of the protein. The addition of pure oxygen to the tonometer during determination of P_{50} caused a decrease in the initial maximum of halothane concentration. As this contributed only a maximum of 2% change, no correction was made for this effect. pH measurements were made at 25 °C in the buffer solutions and at the end of each experiment with a pH electrode and a PHM 62 pH meter calibrated with precision buffer solutions S 1500 and S 1510 (Radiometer, Copenhagen, Denmark). All reagents used in this series of experiments were of analytical grade. Argon and oxygen were of the purest grade available commercially (CFPO, Nanterre, France).

Calculations

Fractional saturation (y) of Hb with oxygen and corresponding Po_2 were calculated as indicated in the appendix. P_{50} and h_{50}, the index of haem–haem interaction at P_{50}, were computed from 5 or 6 points of the mid-portion ($0.3 < y < 0.8$) of the oxygen binding curve according to the Hill equation. The vapour tension of halothane at 25 °C was calculated from the Antoine equation using the constants given by Rodgers and Hill (1978) and was 39.9 kPa for halothane-saturated argon. The solubility coefficient of halothane in aqueous solution was taken from Steward and others (1973) and Allott and colleagues (1973). Statistical analysis was performed with Student's *t* test and *P* values estimated according to Schwartz (1963).

RESULTS

The P_{50} results and the influence of halothane at a partial pressure of 40 kPa are shown in table I. At this high partial pressure, halothane induced an increase in P_{50} (decreased oxygen affinity) of approximately 25% compared with values obtained in its absence. This increase was similar in the four conditions of pH and sodium chloride concentrations, which indicated that this effect was not dependent upon pH or ionic strength. Indeed, the value of the alkaline Bohr effect estimated as the difference of log P_{50} between pH 7.0 and pH 8.0 was similar whether halothane was present or not. In the four conditions the binding of oxygen to Hb remained satisfactory in the presence of halothane and similar to that observed with argon. The effect of halothane was reversible, since a solution of deoxy-Hb previously equilibrated for 1 h with a halothane–argon gas mixture had a P_{50} value identical to that determined in the absence of halothane when washed for 15 min with pure argon.

The results demonstrate the differential binding of halothane to deoxy- and fully oxygenated Hb. The increase in P_{50} indicates that deoxy-Hb has a

TABLE I. *Mean values of* P_{50} *(kPa) measured in purified haemoglobin solutions in the presence of argon and of halothane*

	Sodium chloride 10 mmol litre^{-1}		Sodium chloride 100 mmol litre^{-1}	
	pH 7.0	pH 8.0	pH 7.0	pH 8.0
Argon 100 kPa				
P_{50}	0.33±0.01	0.13±0.01	0.89±0.03	0.29±0.02
n	9	6	7	7
h_{50}	2.8	2.9	2.9	2.8
Argon + halothane 40 kPa				
P_{50}	0.41±0.02	0.18±0.01	1.10±0.02	0.36±0.01
n	8	5	9	9
h_{50}	2.7	2.70	2.70	2.6
P	⩽0.001	⩽0.001	⩽0.001	⩽0.001

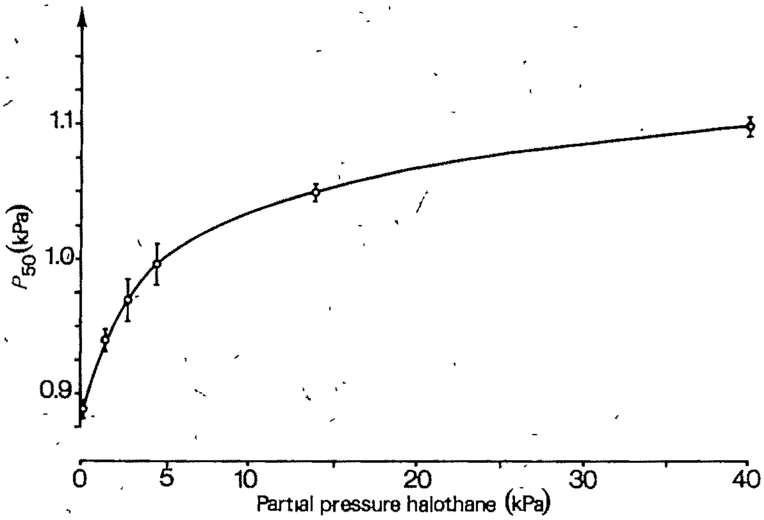

FIG. 1. Changes in P_{50} (kPa) of purified Hb solutions at increasing partial pressures of halothane diluted in argon. Conditions were: Hb concentration 0.16 mmol litre^{-1} tetramer. pH 7.0, 25 °C, bis Tris 50 mmol litre^{-1} and sodium chloride 100 mmol litre^{-1} Open circles are the means of four experiments ± SEM.

greater affinity for halothane than HbO_2 (Antonini and Brunori, 1971).

P_{50} of Hb solutions were measured under various concentrations of halothane to determine if this effect could be demonstrated at partial pressures similar to those used clinically. Figure 1 illustrates the dependence of P_{50} upon the partial pressure of halothane. The hyperbolic shape of this curve indicates a saturating mechanism for oxygen-linked binding of halothane to Hb. These results allow estimation of the amount of halothane released from Hb per mole of haem oxygenated. According to the linked-function relationship (Wyman, 1964) this is obtained from the ratio $\Delta \log P_{50} / \Delta \log$ [halothane] mmol litre^{-1} provided that the oxygen binding curves remain symmetrical in the presence of the factor concerned, and is halothane 0.05 mol per mol haem oxygenated. This quantity is small compared with other factors such as chloride, 0.5 mol at pH 7.0 (Guesnon et al., 1979). From the value of the upper asymptote estimated from the curve shown in figure 1, a Hill plot can be drawn relating the logarithm of the fractional effect to the logarithm of the concentration of halothane (fig. 2). The plot is linear with a slope of unity. The overall apparent association constant of oxygen-linked halothane (Ka) is 3.2 mmol^{-1}. This is about half that estimated for butene binding (Poyart et al., 1979) and much less than that of chloride ions

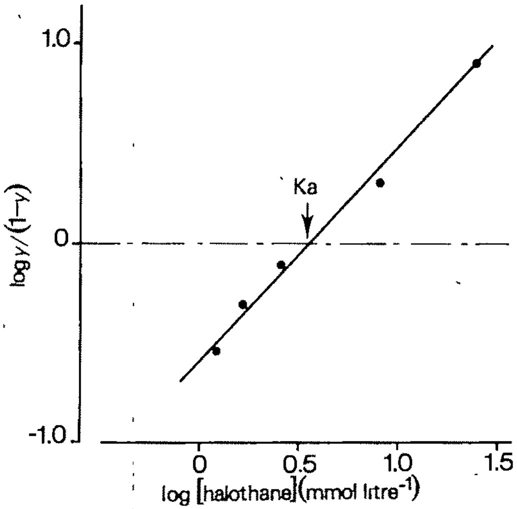

FIG. 2. Hill plot illustrating the fractional changes of P_{50} against the concentration of halothane taken from the values of figure 1. Ka is the apparent overall binding constant of oxygen-linked halothane to Hb and amounts to 3.2 mmol^{-1}. The slope of the Hill plot is unity.

(13 mmol^{-1}) (Guesnon et al., 1979) or 2, 3-DPG binding (280 mmol^{-1}) (Benesch et al., 1971).

DISCUSSION

The mechanism involved in the binding of halothane to Hb cannot be demonstrated with certainty from our results. These show, however, that the mechanism does not seem to involve electrostatic interactions as it is independent of pH and of ionic strength. Hydrophobic interactions may cause this effect as discussed for dichloromethane (Schoenborn and North, 1978), butene (Poyart et al., 1979) and halothane (Barker et al., 1975). A slope of unity of the Hill plot in figure 2 indicates that oxygen-linked halothane binds to one single binding site or, more likely, to several identical sites on the Hb tetramer. These binding sites should lie in the interior of the polypeptide chains which are lined with hydrophobic side-chain residues. This might be at the $\alpha_1\beta_2$ interface as advocated for dichloromethane binding by Schoenborn and North (1978) from x-ray diffraction studies, or possibly also in the highly hydrophobic haem pocket (Perutz, 1976). In the latter hypothesis, halothane molecules would alter, through some steric hindrance, the changes in geometry of the haem link to oxygen. Arnone (1974) recognized the presence of a carbon dioxide molecule in a hydrophobic hole to the rear of the β haem group in an x-ray study of crystalline human deoxy-Hb equilibrated at $P\text{CO}_2$ 100 kPa.

In conclusion, we have demonstrated the oxygen-linked character of halothane binding to human adult Hb. We suggest that this binding involves hydrophobic interactions within Hb because of the independence of the effect of pH or anion concentration. The effects of halothane appear of minor importance in oxygen binding to Hb *in vivo* compared with other factors acting through electrostatic interactions. The results provide another example of a reversible allosteric effect on Hb acting through nonelectrostatic interactions. This mechanism may account also for the effect of halothane on other proteins, especially enzymes such as glutamate dehydrogenase, the function of which is reported to be altered in the presence of halothane (Brammal, Beard and Hulands, 1973).

APPENDIX

The fractional saturation of Hb with oxygen was calculated from:

$$y = \frac{(A_{x576\,5} - A_{d576\,5}) + (A_{d560} - A_{x560})}{(A_{o576\,5} - A_{d576\,5}) + (A_{d560} - A_{o560})}$$

where A = absorbance at the indicated wavelengths; subscripts d and o refer to deoxy- and fully oxygenated Hb and x to partially oxygenated Hb.

The partial pressure of oxygen (P) in the equilibrium vessel and resulting from addition of a known volume (v') of dry oxygen at room temperature is given by:

$$P = \left\{\frac{P_B \times v'}{V - v}\right\} \frac{T}{T}$$

where P_B = barometric pressure; V = volume of the precisely calibrated glass vessel; v = volume of the liquid phase; T' and T = temperature of the solution (298 K) and of the gas introduced into the vessel.

ACKNOWLEDGEMENTS

The authors are indebted to C. Gautheron and J. Grellier for their help in preparing the manuscript. This work was supported by funds from INSERM C. L. 78.5.058.

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FIXATION DE L'HALOTHANE A L'HEMOGLOBINE DUE A L'OXYGENE CHEZ L'HOMME ADULTE

RESUME

On a mesuré l'affinité de solutions d'hémoglobine (Hb) d'homme adulte normal pour l'oxygène en présence de concentrations croissantes d'halothane. Nous avons observé une augmentation maximale de 25% du P_{50} avec 40 kPa d'halothane comparée au contrôle (mélanges gazeux oxygéne–argon) qui démontrait que la fixation de l'halothane à la molécule Hb est liée à la présence d'oxygène. L'effet de l'halothane sur le P_{50} était indépendant du pH entre 7,0 et 8,0 et de la concentration de chlorure entre 10 et 100 mmol litre^{-1}. Ceci amène à penser que les interactions halothane–Hb peuvent s'effectuer à travers une liaison hydrophobique semblable à celle qui s'effectue avec les hydrocarbures aliphatiques de chaîne courte. La fixation de l'halothane due à l'oxygène semble de moindre importance dans la modification de la fixation de l'oxygène à l'Hb *in vitro vis-à-vis* d'autres facteurs tels que l'ion chlorure ou le DPG-2,3 (diphosphoglycérate).

SAUERSTOFFGEBUNDENE BINDUNG VON HALOTHAN AN HÄMOGLOBIN BEIM ERWACHSENEN MENSCHEN

ZUSAMMENFASSUNG

Die Affinität für Sauerstoff der Lösungen von Hämoglobin (Hb) aus normalen erwachsenen Menschen wurde im Beisein von zunehmenden Konzentrationen von Halothan gemessen. Wir beobachteten eine maximale Zunahme der P_{50} um 25% mit Halothan 40 kPa, verglichen mit Kontrollen (Sauerstoff–Argon-Gasmischungen), was die sauerstoffgebundene Natur der Bindung von Halothan an das Hb-Molekul andeutet. Die Wirkung von Halothan auf P_{50} war unabhängig von pH werten zwischen 7.0 und 8.0 und von Chloridkonzentrationen zwischen 10 und 100 mmol litre^{-1}. Es liegt also nahe, dass Halothan–Hb-Wechselwirkungen infolge hydrophober Verkettungen auftreten könnten, wie es auch bei aliphatischen Kohlenwasserstoffen mit kurzen Ketten der Fall sein kann. Die sauerstoffgebundene Bindung von Halothan scheint bei der Änderung der Sauerstoffbindung an Hb *in vivo* eine untergeordnete Rolle zu speilen, verglichen mit anderen Faktoren wie z.b. Chloridion oder 2,3-Diphosphoglycerat.

FIJACION DEL HALOTANO RELACIONADA CON EL OXIGENO A LA HEMOGLOBINA DEL SER HUMANO ADULTO

SUMARIO

Se midió la afinidad al oxigeno de soluciones de hemoglobina (Hb) de ser humano adulto normal, en presencia de crecientes concentraciones de halotano. Observamos un aumento máximo del P_{50} de une 25% con 40 kPa de halotano, en comparación con el control (mezclas gaseosas de oxigeno–argón), lo que indica que la fijación del halotano a la molécula Hb se relaciona con el oxígeno. El efecto del halotano sobre el P_{50} era independiente del pH entre 7,0 y 8,0, así como de la concentración de cloruro entre 10 y 100 mmol litro^{-1}. Esto hace pensar que las interacciones halotano–Hb pueden ocurrir a través del encadenamiento hidrofóbico, tal como sucede con los hidrocarburos alifáticos de cadena corta. La fijación del halotano relacionada con el oxígeno parece tener menor importancia en la modificación de la ligazón del oxigeno al Hb *in vitro*, en comparación con otros factores tales como el ión de cloruro o el DPG-2,3 (difosfoglicerato).

Br. J. Anaesth. (1980), 52, 1183

DIFFERENTIAL NERVE BLOCK BY BUPIVACAINE AND 2-CHLOROPROCAINE

An experimental study

P. H. ROSENBERG, E. HEINONEN, S.-E. JANSSON AND J. GRIPENBERG

SUMMARY

The differential blocking effect of bupivacaine and 2-chloroprocaine was studied on isolated rabbit cervical sympathetic trunks (B and C fibres) and phrenic nerves (A fibres). The B fibres (myelinated, preganglionic) were more sensitive than C fibres (unmyelinated, postganglionic) to nerve block by bupivacaine and 2-chloroprocaine, as assessed by changes in action potential amplitude and latency. The blocking action of both bupivacaine and 2-chloroprocaine caused a decrease in amplitude in the B fibres approximately twice as great as that produced in the C fibres. In similar experimental conditions, the fastest conducting A fibres (myelinated, motor) were least affected. Bupivacaine 200 μmol litre^{-1} completely blocked all B fibres in 7 min and C fibres in 10 min. The average action potential amplitude of A fibres at that time was 78%. 2-Chloroprocaine 300 μmol litre^{-1} completely blocked B fibres in 4 min and C fibres in 15 min. At 15 min the average action potential amplitude of the A fibres was still approximately 35%. Although these two local anaesthetics differ structurally and physico-chemically, the rates of block of the different fibres were in the same order *in vitro*.

Fifty years ago cocaine was shown to block small myelinated A fibres more effectively than thicker ones (Gasser and Erlanger, 1929), a finding which suggests a direct relationship between local anaesthetic blocking effect and nerve fibre size. This relationship does not seem to be valid when different groups of fibres are compared; lower concentrations of local anaesthetics are needed to block A delta fibres (1–4 μm in diameter) than the smaller C fibres (unmyelinated, 0.5–1 μm in diameter) (Nathan and Sears, 1961). Studies with a variety of nerve preparations have suggested that B fibres (myelinated, 1–3 μm in diameter) may be blocked more rapidly than A fibres by procaine (Crescitelli, 1952) and more rapidly than A and C fibres by lignocaine (Ritchie, Ritchie and Greengard, 1965). More recently, Heavner and de Jong (1974) showed convincingly that B fibres of rabbit cervical sympathetic trunks were about three times more sensitive than C fibres to lignocaine, which supported the clinical impression of an extensive and significant block of sympathetic fibres preceding maximal spread and potency of analgesia in spinal or extradural anaesthesia (Greene, 1958; Covino and Vasallo, 1976).

Bupivacaine and 2-chloroprocaine are frequently used in obstetric extradural analgesia, particularly because of their low fetal toxicity (Ralston and Shnider, 1978). Another advantage of bupivacaine is a clinically observed differential blockade with good sensory block and a low degree of motor block (Bromage, 1978), while further advantages of 2-chloroprocaine are principally rapid onset and short duration of the block because of the rapid rate of hydrolysis (Foldes et al., 1965).

As these two local anaesthetics are quite different in structure and clinical action, but are often used for similar purposes, their individual blocking properties on B and C fibres and on the largest A fibres of the rabbit were evaluated.

METHODS

Nerve preparations

Adult rabbits were sacrificed and both cervical sympathetic trunks, from the thoracic inlet to the superior cervical ganglion, were rapidly removed. Stretching and compression were carefully avoided and the dissection field was kept moist using a spray of Ringer solution. The trunks were cleared of excessive connective tissue, but the

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0007-0912/80/121183-07 $01.00

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nerve sheaths were left intact. The cervical sympathetic trunks contain predominantly myelinated preganglionic B fibres and unmyelinated postganglionic C fibres, and apparently no A fibres (Bishop and Heinbecker, 1932; Heavner and de Jong, 1974).

Phrenic nerve preparations, which comprise a great number of myelinated motor A fibres were obtained from another group of rabbits. The sheaths were not removed from these nerves.

Nerve chamber and electrical stimulation

The nerves were immersed in Ringer solution equilibrated with 95% oxygen and carbon dioxide 5% in a plexiglass chamber of about 5 ml capacity. The composition of the solution (mmol litre^{-1}) was: NaCl 136, KCl 5.6, $CaCl_2$ 2.2, $MgCl_2$ 1.3, $NaHCO_3$ 16.2, $NaH_2PO_4/Na_2\ HPO_4$ 1.3 and D-glucose 11.0; pH 7.4 (37 °C). The nerve preparation was continuously perfused with fresh solution from a peristaltic pump at a flow of 5 ml min^{-1}. The temperature of the chamber solution was maintained at 35.7–37.2 °C by water circulating in the jacket surrounding the chamber. One end of the nerve trunk was placed on a bipolar stimulation electrode, which was isolated from the Ringer solution by a latex rubber septum (perforated for the nerve) and liquid paraffin. The other end of the trunk was fixed by miniature needles to a paraffin base plate. The action potentials were recorded extracellularly by glass microelectrodes which were filled with potassium chloride 3 mol litre^{-1} (DC resistance 5–12 MΩ).

The nerves were stimulated electrically with square wave pulses of 0.15 ms duration. B and C fibre action potentials from the sympathetic trunks were elicited by supramaximal pulses (10–30 V, twice the voltage giving maximal C action potential) and were viewed simultaneously on the oscilloscope. The action potential responses of the fastest conducting A fibres of phrenic nerves were obtained by supramaximal 1–3 V pulses. The different potentials were identified after amplification by their characteristic propagation velocities (A fibres 40–120 m s^{-1}); B fibres 3–14 m s^{-1}; C fibres 0.2–1.5 m s^{-1}) (Coppin and Jack, 1972). A series of action potentials were AC recorded on a magnetic FM tape recorder at predetermined time intervals for later assessment. Action potential amplitude (peak to peak) and latency (duration from stimulation artefact to first crossing of baseline by action potential depolarization wave) were measured from ink-jet paper recordings after replaying the recorded material at a speed 10 times slower than the recording speed.

The stimulation frequency was 1 Hz during each recording and 0.1 Hz between recordings.

Drugs and test procedure

The local anaesthetics tested were bupivacaine hydrochloride (Astra, Södertälje, Sweden) and 2-chloroprocaine hydrochloride (Pennwalt Corp., Rochester, New York, U.S.A.).

The local anaesthetic solutions were prepared immediately before each experiment in freshly made and oxygenated (95% oxygen and 5% carbon dioxide) Ringer solution.

The nerves were allowed 30–45 min to adapt before the recording of control action potentials and application of drugs. Perfusion with local anaesthetic solutions continued for 20 min (including experiments in which the action potentials completely disappeared in a shorter time) and recordings were made at each full minute up to 10 min, at 15 min and 20 min. The perfusion fluid was then changed to drug-free Ringer solution and recovery from the block was followed by recording action potentials every 5 min for 30 min, followed by a final recording at 45 min. Recovery was considered to have occurred when the action potential amplitude exceeded 85% of the control amplitude. Two concentrations of the local anaesthetics were used in random order for each nerve. The highest drug concentrations were tested on three different nerve preparations and all other concentrations on at least four preparations.

RESULTS

The effect of bupivacaine 25, 50, 100 and 200 μmol litre^{-1} on the peak-to-peak amplitude of B and C fibres is shown in figures 1A and 1B. Although the response to 25 μmol litre^{-1} bupivacaine was negligible, the decrease in the action potential amplitude was apparent when the concentration was increased to 50 μmol litre^{-1} or more. In B fibres there was a sharp change in response between the two lowest concentrations, while in C fibres the effects of 50 and 100 μmol litre^{-1} could not be separated. In all preparations, bupivacaine at 200 μmol litre^{-1} abolished the action potential of sympathetic B fibres in 7 min and of C fibres in 10 min. In the phrenic nerve preparations, the highest bupivacaine concentration produced a mean decrease in the A fibre action potential to

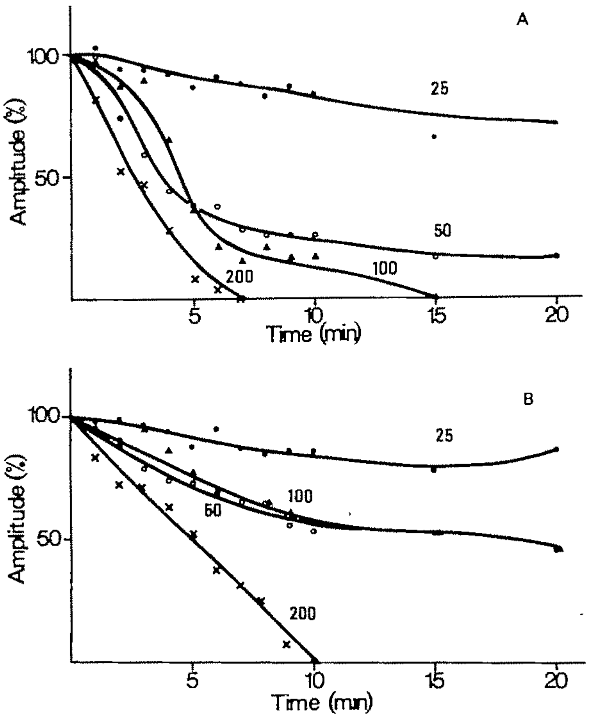

FIG. 1. Effect of bupivacaine 25 (●), 50 (○), 100 (▲) and 200 (×) μmol litre^{-1} on action potential amplitude in rabbit cervical sympathetic trunk B (A) and C (B) fibres. Each point is the mean of four or five experiments (with 200 μmol litre^{-1}, three experiments). The results indicate percentages of control.

45% of control in 20 min (fig. 2). After 10 min, when the C fibre potentials disappeared, the action potential amplitude of the fastest A fibres had decreased to a mean level of 78%. When immersed in drug-free medium, the recovery from bupivacaine-induced block took 30–45 min, which is comparatively slow.

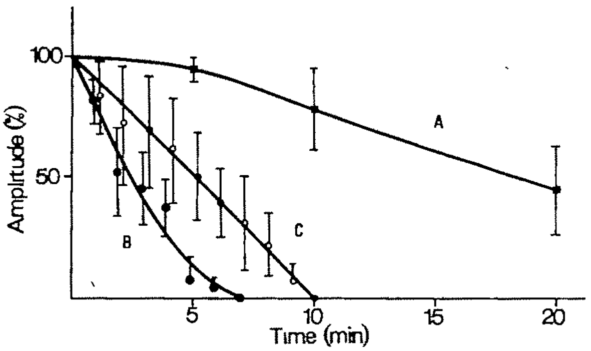

FIG. 2. The effect of bupivacaine 200 μmol litre^{-1} on the action potential amplitude in A, B and C fibres. 100% = control. Means ± SEM of at least three experiments.

2-Chloroprocaine 50 μmol litre^{-1} produced only a slight mean decrease in the action potential amplitude of B fibres (fig. 3A) and even a concentration of 100 μmol litre^{-1} had no significant effect on C fibres (fig. 3B). As with bupivacaine, B fibres appeared to be more rapidly blocked than C fibres,

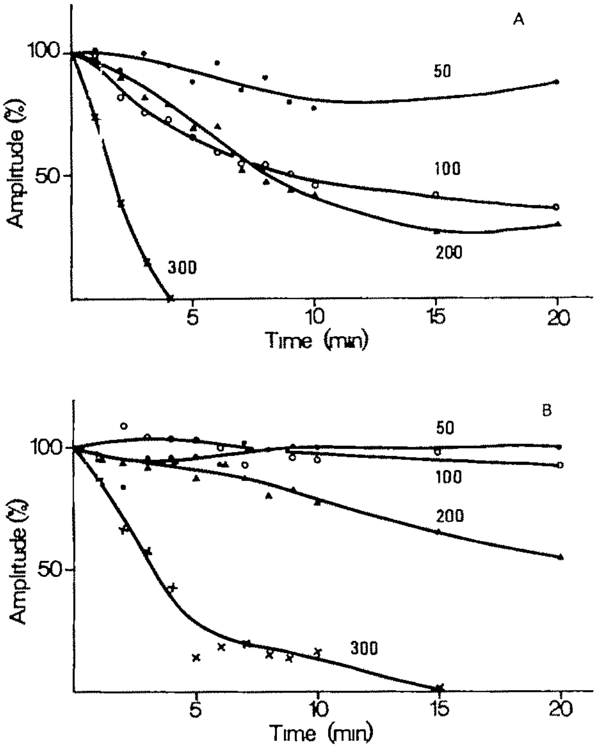

FIG. 3. Effect of 2-chloroprocaine 50 (●), 100 (○), 200 (▲) and 300 (×) μmol litre^{-1} on action potential amplitude in rabbit cervical sympathetic trunk B (A) and C (B) fibres. Each point is the mean of four or five experiments (with 300 μmol litre^{-1}, three experiments).

as determined by changes in amplitude, latency (duration from stimulation artefact to first crossing of baseline by action potential depolarization wave) and action potential duration (at baseline, fig. 4). 2-Chloroprocaine 300 μmol litre^{-1} totally abolished all B fibre action potentials in 4 min and those of all C fibres in 15 min. By the time all C fibre action potentials had disappeared, approximately 35% of the A fibre action potentials still remained. When 2-chloroprocaine 300 μmol litre^{-1} was applied to phrenic nerves, the action potential amplitude of the A fibres decreased to a mean level of 20% in 20 min (fig. 5). Compared with the rather slow recovery of the nerves in experiments with bupivacaine, the recovery after

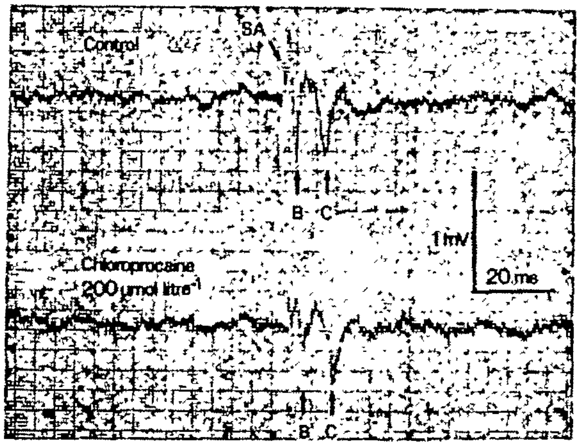

FIG. 4. Original recordings from one experiment with 2-chloroprocaine 200 μmol litre^{-1}. In the upper tracing (control) immediately after the stimulation artefact (SA) there is a sharp B fibre potential (B) followed by a broader C fibre potential (C). In the lower tracing, 5 min after drug application, the B fibre potential has decreased to about half the original value and its latency has increased, while the C fibre potential appears unchanged.

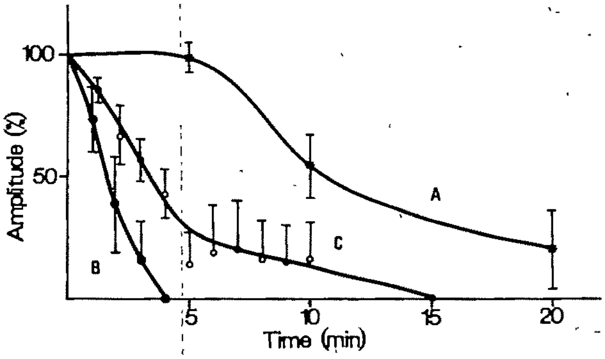

FIG. 5. The effect of 2-chloroprocaine 300 μmol litre^{-1} on the action potential amplitude in A, B and C fibres. 100% = control. Means ± SEM of at least three experiments.

2-chloroprocaine treatment was in most cases rapid at the beginning of the washing, with complete restoration of the amplitudes in 10–15 min.

Both local anaesthetics had a clear effect on the latency of the action potentials of B and C fibres. The latency was increasingly prolonged with time during treatment with the drugs, parallel to the decrease in amplitude. Although the differences were not statistically significant, the latency of B fibre action potentials increased before that of C fibre action potentials (fig. 6). The latencies showed large variations, which is expected since conduction velocity in nerves is influenced by a variety of factors including occurrence of myelin, time-dependence of ionic currents, fibre diameter, membrane capacitance and membrane resistance (Dudel, 1975). In those cases where the B fibre potential was abolished and C fibre potential remained, the maximum measurable increase in latency 20 min after the start of treatment ranged from 1.5 to 2.8 times that of control latency.

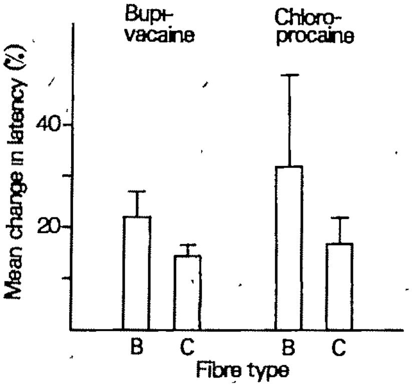

FIG. 6. Mean changes (Δ%), compared with control, in latency (duration of impulse from stimulation artefact to first crossing of baseline by action potential) produced by bupivacaine 100 μmol litre^{-1} or 2-chloroprocaine 200 μmol litre^{-1} after 5 min of treatment. Means ± SEM of at least four experiments.

The mean decrease in action potential amplitude at the same drug concentration may be compared to obtain an approximate estimate of the potency difference of the drugs between B and C fibres. After 5 min, bupivacaine 100 μmol litre^{-1} caused a 62% decrease in B fibres and a 27% decrease in C fibres (2.3 times difference) while with 200 μmol litre^{-1} the corresponding percentages were 92% and 50% (1.8 times difference, figs 1A, B). Also, after 5 min, 2-chloroprocaine 200 μmol litre^{-1} caused a 30% decrease in action potential amplitude in B fibres and a 13% decrease in C fibres (2.3 times difference).

Comparing the effects of bupivacaine 200 μmol litre^{-1} and 2-chloroprocaine 200 μmol litre^{-1} showed that, 5 min after the start of treatment, both B and C fibres were more strongly blocked by bupivacaine than by 2-chloroprocaine. The relative decrease in amplitude was about three times greater after bupivacaine in both fibre types.

DISCUSSION

The present study showed that B fibres (myelinated preganglionic fibres) were the most sensitive of the three major nerve groups to bupivacaine and

2-chloroprocaine. The differential effect on B and C fibre action potential amplitudes is in agreement with earlier *in vitro* studies with lignocaine (Heavner and de Jong, 1974). The conduction velocity, measured as latency of the action potentials, was also affected differently in B and C fibres; when the partially blocked potentials were observed simultaneously, the B fibre latency was more prolonged than that of C fibres.

When equimolar concentrations of bupivacaine and 2-chloroprocaine were compared, bupivacaine was found to be about three times as potent as 2-chloroprocaine in B and C fibres. Although the A fibre potentials were studied with only one concentration of each local anaesthetic, the results suggest that, in *in vitro* conditions, the potency difference of bupivacaine and 2-chloroprocaine compared on the fastest A fibres may not be significant. A direct comparison with *in vivo* or clinical conditions is hindered by the different kinetic profiles of these local anaesthetics, but animal experiments and clinical studies indicate that bupivacaine is four to eight times as potent as 2-chloroprocaine (Covino and Vasallo, 1976).

In our *in vitro* study, the potency difference may primarily have been governed by differences in lipid solubility and rate of penetration of the drugs. At lower concentrations it appears that the protein binding of bupivacaine and 2-chloroprocaine is about equal (Nishimura et al., 1975), while bupivacaine is more lipid-soluble than 2-chloroprocaine (Covino and Vasallo, 1976). This characteristic of bupivacaine, with its lower pK_a (8.1 compared with 8.7 for 2-chloroprocaine at 25 °C) (Ralston and Shnider, 1978) indicate a lower degree of ionization at physiological pH, suggesting that bupivacaine penetrates nerve sheaths and plasma membranes more easily than does 2-chloroprocaine. This may influence sodium channels more effectively by either of the suggested major local anaesthetic action mechanisms; "binding to sodium channel from inside of nerve membrane" or "membrane expansion" (Ritchie, 1975).

The reason for the high sensitivity of B fibres to local anaesthetics remains a matter of speculation. These fibres are myelinated and thus, at least in the case of highly lipid-soluble local anaesthetics like bupivacaine, the attraction to myelin lipids may be related to potency. An interesting hypothesis was discussed by Heavner and de Jong (1974), who suggested that fewer anaesthetic molecules would be needed to block sodium channels in B fibres because the action potential is generated only at the nodes of Ranvier and the conduction of excitation is saltatory (Dudel, 1975). The nodal region has been shown to function as a specialized acceptor site for cations (Landon and Langley, 1971), and probably attracts charged cationic anaesthetic molecules as well. In nodal membrane preparations, the sodium conductivity has been significantly inhibited by local anaesthetic molecules (Århem and Frankenhaeuser, 1974). The C fibres, however, which lie invaginated in grooves of Schwann cell membranes, conduct the action potential along the length of the nerve. This protection and lack of specialized excitation areas in C fibres might explain why they are more resistant to local anaesthetic block than the B fibres. The fibres do not differ only in their response to local anaesthetics. C fibres also seem to be more resistant to ischaemic compression than larger myelinated fibres (Fowler and Ochoa, 1975) and more resistant to cold block than the smallest A delta fibres (Douglas and Malcolm, 1955; Paintal, 1965).

The fact that the fastest conducting (largest) A fibres were less sensitive than B and C fibres to block by bupivacaine and 2-chloroprocaine in our study is probably because of fibre size. In large A fibres the internodal distance may be as great as 1.6 mm (Coppin and Jack, 1972) which would theoretically indicate that at least 3.2–3.5 mm of an axon length (three adjacent nodes) (Tasaki, 1953) must be reached by the local anaesthetic solution to block conduction. Since we used phrenic nerve trunks made up of numerous axons, we apparently did not achieve a steady state block in all A fibres in the treatment period of 20 min (figs 2 and 5). There may also have been additional slowing of diffusion by the sheaths of the nerve trunk, particularly by the perineural barrier (Feng and Liu, 1949).

ACKNOWLEDGEMENTS

This study was supported by a grant from The Signid Juselius Foundation, Finland. The fruitful advice and criticism by Dr J. E. Heavner is gratefully acknowledged. We are indebted to Håkan Edstrom, PH.D., Astra, Södertalje, Sweden, for providing us with bupivacaine hydrochloride.

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BLOCAGE NERVEUX DIFFERENTIEL PAR LA BUPIVACAINE ET LA CHLOROPROCAINE-2

Une étude expérimentale

RESUME

On a procédé à l'étude de l'effet de blocage différentiel de la bupivacaine et de la chloroprocaine-2 sur des troncs sympathiques cervicaux (fibres B et C) et des nerfs phréniques (fibres A) isolés de lapin. Les fibres B (myélinées, préganglionaires) étaient plus sensibles au blocage nerveux par la bupivacaine et la chloroprocaine-2 que les fibres C (non myélinées, postganglionaires), ainsi que révélé par l'évaluation des modifications de l'amplitude du potentiel d'action et de la latence. L'action de blocage tant de la bupivacaine que de la chloroprocaine-2 a provoqué une diminution de l'amplitude dans les fibres B deux fois plus forte approximativement que celle enregistrée dans les fibres C Dans des conditions expérimentales analogues, les fibres A conductrices les plus rapides (myélinées, moteur) étaient les moins affectées. Deux cent μmol litre^{-1} de bupivacaine ont bloqué complètement toutes les fibres B en 7 min et les fibres C en 10 min. L'amplitude moyenne du potential d'action des fibres A était a ce moment-là de 78%. Trois cent μmol litre^{-1} de chloroprocaine-2 bloquèrent complètement les fibres B en 4 min et les fibres C en 15 min. Au bout de 15 min, l'amplitude moyenne du potentiel d'action des fibres A était encore de 35% environ. Bien que ces deux agents anesthésiques diffèrent du point de vue structurel et physico-chimique, les rythmes de blocage des diverses fibres suivaient le même ordre *in vitro*.

DIFFERENTIALNERVENBLOCKADE DURCH BUPIVACAINE UND 2-CHLOROPROCAINE

Eine Experimentelle Studie

ZUSAMMENFASSUNG

Die Differentialblockierungseffekt von Bupivacaine und 2-Chloroprocaine wurde bei isolierten zervikalen sympathischen Hauptstrangen (B und C Fasern) und beim Phrenikus (A Fasern) von Kanichen studiert. Die B Fasern (myeliniert, präganglionär) waren einer Nervenblockade durch Bupivacaine und 2-Chloroprocaine gegenuber empfindlicher als die C Fasern (unmyeliniert, postganglionär), gemessen an den Änderungen in der Aktionspotentialamplitude und Latenz. Die blockierende Wirkung von sowohl Bupivacaine als auch 2-Chloroprocaine führte eine Verminderung der Amplitude bei den B Fasern herbei, die ungefähr zweimal so stark wie bei den C Fasern war. Unter ähnlichen experimentellen Bedingungen wurden die am schnellsten leitenden A Fasern (myeliniert, motorisch) am wenigsten beeinflusst. Bupivacaine 200 μmol litre^{-1} verursachte eine totale Blockade samtlicher B Fasern innerhalb 7 Minuten und C Fasern innerhalb 10 Minuten. Die durchschnittliche Aktionspotentialamplitude von A Fasern zu dieser Zeit betrug 78%. 2-Chloroprocaine 300 μmol litre^{-1} blockierte sämtliche B Fasern innerhalb 4 Minuten und C Fasern innerhalb 15 Minuten. Nach 15 Minuten betrug die durchschnittliche Aktionspotentialamplitude der A Fasern immer noch ca. 35%. Obwohl diese zwei Lokalanästhesiemittel strukturell und physisch-chemikalisch verschieden sind, lagen die Blockierungsgeschwindigkeiten der verschiedenen Fasern *in vitro* in der selben Grössenordnung.

BLOQUEO DIFERENCIAL DE LOS NERVIOS POR BUPIVACAINA Y CLOROPROCAINA-2

Un estudio experimental

SUMARIO

Se estudió el efecto bloqueador diferencial de la bupivacaina y de la cloroprocaina-2 en troncos simpáticos cervicales (fibras B y C) y nervios frénicos (fibras A) aislados de conejo. Las fibras B (mielinadas, pregangliónicas) eran más sensibles al bloqueo nervioso por bupivacaina y cloroprocaina-2 que las fibras C (no-mielinadas, postgangliónicas), según consta por los cambios de amplitud del potencial de acción y de latencia. La acción bloqueadora de la bupivacaina y de la cloroprocaina-2 causó en las fibras B una disminución de amplitud dos veces mayor aproximadamente de la producida en las fibras C. En condiciones experimentales análogas, las fibras A conductoras más veloces (mielinadas, motoras) fueron menos afectadas. Doscientos μmol litro^{-1} de bupivacaina bloquearon totalmente a todas las fibras B en 7 min y a las fibras C en 10 min Al momento, la amplitud media del potencial de acción de las fibras A era de 78% Trescientos μmol litro^{-1} de cloroprocaina-2 bloquearon completamente a las fibras B en 4 min y a las fibras C en 15 min. A los 15 min, la amplitud media del potencial de acción de las fibras A era aún 35% aproximadamente Aunque estos dos agentes anestéticos difieren desde el punto de vista estructural y físico-químico, los ritmos de bloqueo de las distintas fibras seguían el mismo orden *in vitro*.

Br. J. Anaesth. (1980), 52, 1191

CHANGES IN THE RESPIRATORY PATTERN INDUCED BY HALOTHANE IN THE CAT

T. NISHINO AND Y. HONDA

SUMMARY

The effect of halothane on the respiratory pattern was investigated in lightly anaesthetized cats. Following the administration of 2.0% halothane there was a transient increase in respiratory frequency because of a decrease in the duration of expiration, followed by a progressive decrease in respiratory frequency as a result of prolongation of inspiration; both events could be demonstrated before and after vagotomy. During the steady state obtained following the administration of 0.5, 1.0 and 1.5% halothane and after vagotomy there was a decrease in the duration of expiration and a progressive increase in the duration of inspiration. Tidal phrenic output decreased progressively as the concentration of halothane was increased. These results suggest that changes in respiratory pattern seen during halothane anaesthesia might involve some excitatory central mechanisms other than the bulbopontine system.

Tachypnoea develops during halothane anaesthesia, although halothane depresses ventilation (Severinghaus and Larson, 1965), and has been attributed to the sensitization of the pulmonary stretch receptor (Dundee and Dripps, 1957; Coleridge et al., 1968). However, several studies have shown (Ngai, Katz and Farhie, 1965; Paskin, Skovsted and Smith, 1968) that the sensitization of the pulmonary stretch receptor is not essential for the occurrence of tachypnoea during halothane anaesthesia and have suggested that some central excitatory mechanisms are involved. Since there is little current information on the effect of halothane on the central respiratory pattern, we have investigated the changes in the central respiratory pattern induced by the administration of halothane.

METHODS

Seven adult cats (2.0–4.0 kg) were anaesthetized with 2% halothane in oxygen, using a precalibrated vaporizer (Fluotec Mark 2). The trachea was cannulated and both femoral arteries were cannulated to allow withdrawal of arterial blood samples and the measurement of arterial pressure with a transducer–amplifier system. A femoral vein was cannulated also. A phrenic nerve root (C_5) was isolated and prepared for recording of its discharge by a preamplifier–amplifier system (San-ei WM-15). Phrenic nerve activity was amplified by an a.c. amplifier with 100 Hz and 3000 Hz low and high frequency filters. The rectified signal of the amplified signal was integrated by an R–C network having a time constant of 100 ms to obtain a moving average output.

After the surgical preparation of the animal halothane was discontinued and was replaced by α-chloralose 20 mg kg^{-1} i.v. and 60% nitrous oxide in oxygen. The experiment was started at least 40 min after the discontinuation of halothane while the cat was breathing spontaneously. Breathing was monitored with a pneumotachograph (Fleish No. 00) and the tidal volume was obtained by integration of the inspired air flow signal. End-tidal carbon dioxide (PE'_{CO_2}) was monitored with a Beckman carbon dioxide analyser (LB-1). The rectal temperature of the cat was monitored and maintained at 38 °C with a heating lamp.

To study the transient changes in respiratory pattern produced by the administration of halothane in the spontaneously breathing animal, halothane in a concentration of 2.0% in oxygen was administered acutely and continued until the arterial pressure decreased to less than 7 kPa (50 mm Hg). At this point halothane was discontinued. Phrenic nerve activity, moving average output, arterial pressure, tidal volume and PE'_{CO_2} were recorded on a Visicorder (San-ei). Following this experiment bilateral vagotomy was performed and the acute administration of halothane repeated. The cat was paralysed with gallamine

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0007-0912/80/121191-07 $01.00

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3 mg kg^{-1} and the lungs ventilated artificially at a fixed rate and volume (rate × volume = 25 × 40 ml). PE'_{CO_2} was maintained at a slightly hypercapnic value (PE'_{CO_2} = 5.3–6.0 kPa) by introducing a small amount of carbon dioxide into the inspiratory gases. PE'_{CO_2}, phrenic activity, moving average output and arterial pressure were recorded at the following inspired concentrations of halothane: 0%, 0.5%, 1.0% and 1.5%. Each concentration was maintained for 30 min before measurements were made and the order of administration was randomized. At each concentration an arterial blood sample was taken and PO_2, PCO_2 and pH measured using a Radiometer blood-gas analysis system (BMS2 MK2). Since phrenic activity was considered to provide a more direct indication of the timing of the neural activity during the respiratory cycle than measurements involving air flow, the duration of various portions of the respiratory cycle was calculated from the phrenic neurogram. The peak height of the moving average integral per burst was used to quantify the neural respiratory output (fig. 1). For the purpose of comparing various animals, percentage responses of neural tidal and minute outputs were calculated using a value of 100% for the control respiration. Statistical analysis was made with the paired t test.

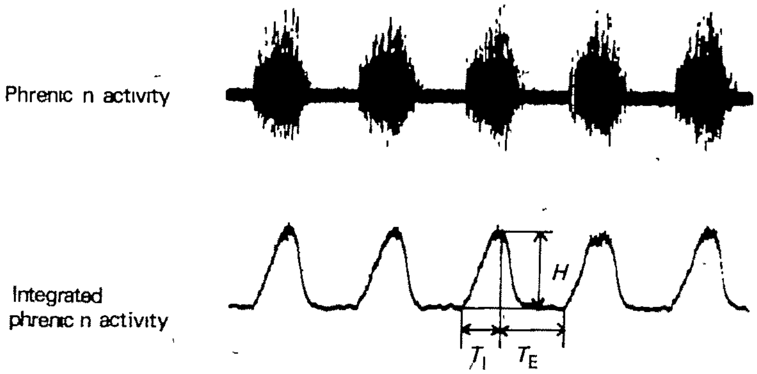

FIG. 1. Definition of inspiratory time (T_I) and expiratory time (T_E). H represents peak height of moving average output per burst.

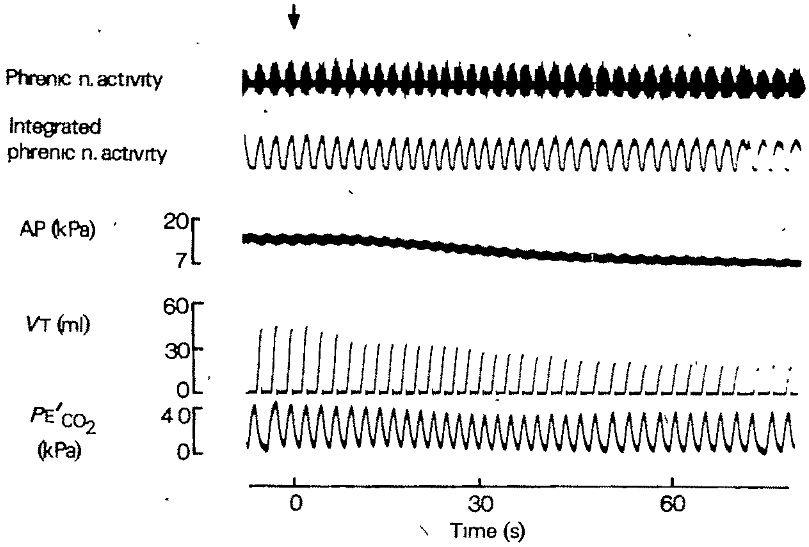

FIG. 2. Transient changes in respiratory pattern following administration of 2% halothane (at arrow) in an intact spontaneously breathing cat. Respiratory frequency increases because of shortening of T_E initially, but it decreases eventually with prolongation of T_I as anaesthesia deepens.

RESULTS

Figure 2 shows the transient changes in respiratory pattern obtained following administration of 2.0% halothane in a spontaneously breathing intact cat. With the start of the administration of halothane arterial pressure decreased. Tidal volume decreased progressively. Respiratory frequency, however, increased transiently and showed a shortening of the duration of expiration with little or no change in the duration of inspiration. After about 40 s respiratory frequency slowed gradually. There was a prolongation of the duration of inspiration as anaesthesia deepened, but there was no increase in the duration of expiration. Similar changes in respiratory pattern occurred after bilateral vagotomy (fig. 3). This suggests that these changes were unaffected by vagal afferent activity. These results were observed in all the animals tested.

An example of the changes in respiratory pattern as a result of halothane in vagotomized and artifically ventilated animals is shown in figure 4. The inspiratory time during control (0% halothane) was 0.7 s and the expiratory time 2.8 s. At 0.5% halothane there was no change in the inspiratory time, but the expiratory time was shortened to 2.2 s. At 1.0% and 1.5% halothane the inspiratory time was prolonged and the expiratory time shortened markedly (fig. 5). There was a significant decrease ($P<0.01$) in the expiratory time at all levels of halothane anaesthesia. In contrast, the inspiratory time did not change at

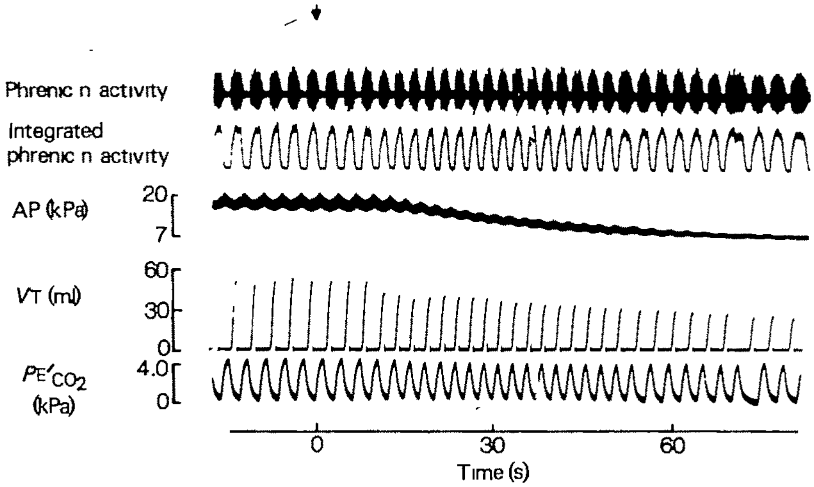

FIG. 3. Transient changes in respiratory pattern following administration of 2% halothane (at arrow) in a spontaneously breathing cat with vagotomy. The same changes in respiratory pattern as observed in figure 2.

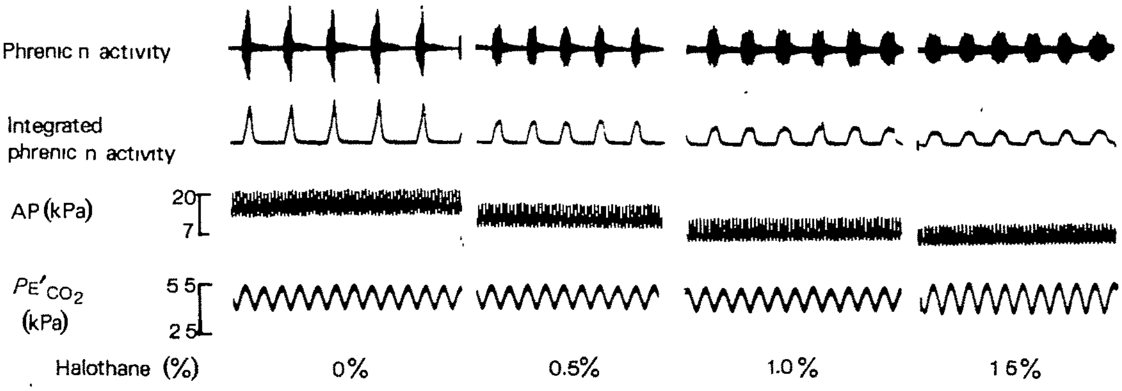

FIG. 4. Changes in respiratory pattern during steady state following halothane administration in an artificially ventilated cat with vagotomy.

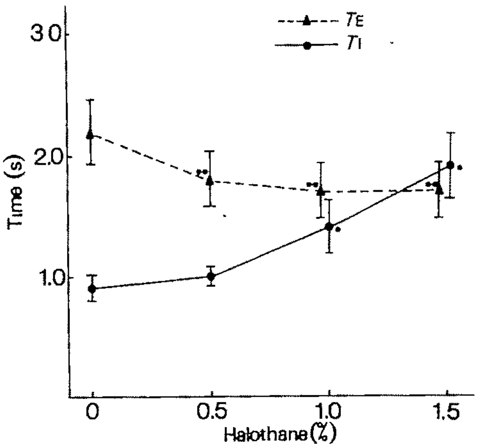

FIG. 5. Effects of halothane on *T*I and *T*E. Values represent mean ± SEM for seven cats. $^{*}P<0.05$; $^{**}P<0.01$, paired *t* test.

0.5% halothane, but it did increase progressively at greater concentration of halothane, namely 1.0% and 1.5%. These changes resulted in an increase in respiratory frequency at light levels of halothane anaesthesia (0.5% halothane) and a decrease in respiratory frequency at deeper levels (fig. 6). In contrast to these changes, tidal phrenic activity decreased consistently with progressive increases in the concentration of halothane (fig. 7). There was no change in minute phrenic activity (calculated from the tidal phrenic activity and respiratory frequency) at 0.5% halothane, but the minute phrenic activity decreased significantly ($P<0.01$) at 1.0% and 1.5% halothane (fig. 8).

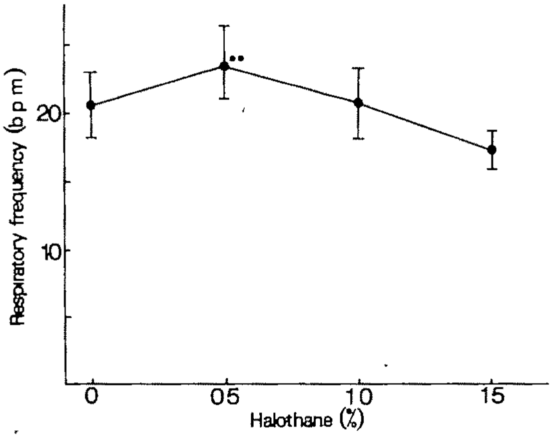

FIG. 6. Effect of halothane on respiratory frequency. Values represent mean ± SEM for seven cats. $^{**}P<0.01$, paired *t* test.

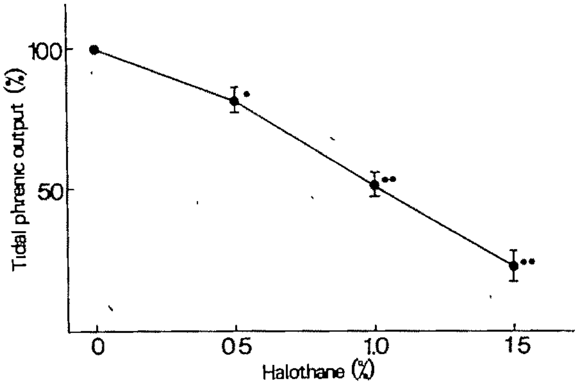

FIG. 7. Effect of halothane on tidal phrenic output (mean ± SEM). $^{*}P<0.05$; $^{**}P<0.01$.

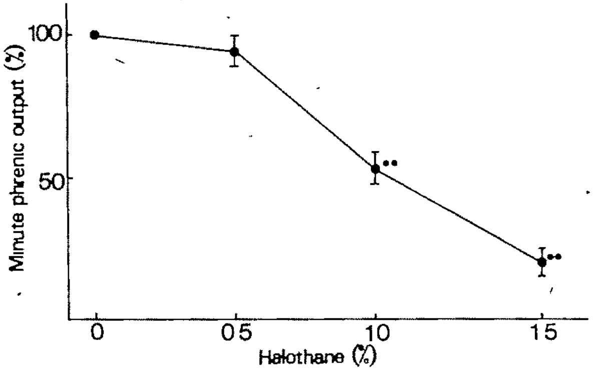

FIG. 8. Effect of halothane on minute phrenic output (mean ± SEM). $^{**}P<0.01$.

Arterial pressure decreased progressively in a dose-related fashion during the administration of halothane. Baseline mean arterial pressure was 20.0 ± 0.7 kPa (150 ± 5.3 mm Hg) (mean ± SEM) during control and 13.3 ± 0.7 kPa (100 ± 5.3 mm Hg) with 0.5% halothane, 10.0 ± 0.5 kPa (75 ± 3.8 mm Hg) with 1.0% halothane and 8.0 ± 0.7 kPa (60 ± 5.3 mm Hg) with halothane 1.5%.

DISCUSSION

α-Chloralose and nitrous oxide are known to cause minimal depression of respiration and circulation (Eckenhoff and Helrich, 1958; Westhues and Fritsh, 1961; Eisele and Smith, 1972), and were used as "background anaesthesia". Since only with a combination of these agents could quiet spontaneous breathing be achieved, neither agents alone providing satisfactory experimental conditions. The influence of the background anaesthesia was minimal and, therefore, the observed changes could be related primarily to the action of halothane.

This study demonstrated that there was an increase in respiratory frequency in the absence of vagal activity during light halothane anaesthesia. This observation is in direct contrast to the idea that halothane can increase respiratory frequency chiefly through increased vagal activity (Kaminski, Karczewski and Gorzynski, 1968) and supports the idea that central mechanisms are involved in the tachypnoea induced by halothane (Ngai, Katz and Farhie, 1965). Detailed analysis of the respiratory patterns revealed that halothane shortened the duration of expiration regardless of the depth of anaesthesia.

Changes in the duration of inspiration, on the other hand, were variable. Under light halothane anaesthesia the inspiratory time was either shortened or prolonged, but under deep halothane anaesthesia it was definitely prolonged. Thus, the linear relation between the inspiratory and the expiratory time reported by Euler and others was not observed during halothane anaesthesia (Clark and Euler, 1972; Euler, 1977). As a result of these changes respiratory frequency increased during light anaesthesia and decreased during deep halothane anaesthesia. These changes are consistent both in the transient state of the spontaneous breathing animal and in the steady state in which ventilation was controlled mechanically and constant blood-gas tensions were maintained. Therefore, changes in chemical stimulants were not crucial in producing the characteristic changes in the respiratory pattern seen with the administration of halothane. Arterial pressure decreased with increasing concentration of halothane and the animals became hypotensive with 1.0% and 1.5% halothane. Hypotension decreases carotid sinus pressure, and thereby decreases baroreceptor activity, but increases chemoreceptor activity (Heymans and Neil, 1958). Since baroreceptor activity inhibits and chemoreceptor activity stimulates breathing, hypotension should stimulate respiration (Lambertsen, 1974). However, hypotension produced by halothane was accompanied always by depression of respiration. This suggests that the contribution of these mechanisms to respiratory changes produced by halothane is negligible.

An increase in the concentration of circulating catecholamines has been known to affect respiration (Coles et al., 1956; Wasserman, Whipp and Castagna, 1974). However, it has been reported (Severinghaus and Larson, 1965; Roisen et al., 1974) that no measurable increase in circulating catecholamines occurs during halothane anaesthesia. Thus, it is unlikely that circulating catecholamines are responsible for the changes in respiratory pattern observed in this study.

Spinal reflexes are known to influence respiratory pattern (Newson Davis, 1974). However, it has been reported (Younes and Youssef, 1978) that halothane does not potentiate such reflexes. Therefore, we do not think that spinal reflex activity affected our results.

There is no doubt that halothane has a dose-related depressant effect on respiration since the tidal output of the phrenic motor neurone activity decreased progressively with increasing depth of halothane anaesthesia. The possibility exists that the mechanism of change in the respiratory pattern noted during the administration of halothane involves only depression of the bulbopontine system. According to the concept of the mechanism for the generation of rhythmicity proposed by Euler (1977), the timing of the respiratory cycle is determined by central inspiratory activity and the off-switch mechanism located presumably in the bulbopontine area. According to this hypothesis tachypnoea can be produced either by a decrease in the threshold of the off-switch mechanism or by an increase in the rate of increase in central inspiratory activity; the respiratory pattern is characterized by a shortening of the inspiratory time since the timing of the inspiratory off-switch event is advanced. In our results an increase in respiratory frequency was associated with shortening of the expiratory rather than inspiratory time. The progressive increase in inspiratory time and decrease in tidal motor neurone output with increasing concentrations of halothane showed rather that halothane depresses the off-switch mechanism in the bulbopontine system. These observations led us to consider that changes in the respiratory pattern with halothane might involve not only the bulbopontine system but other mechanisms in the central nervous system. Magoun and colleagues (1938) have suggested that a certain area in the hypothalamus is thermosensitive and can increase respiratory frequency when its temperature increases. Hugelin and Cohen (1963) have shown that electrical stimulation in the diencephalic and mesencephalic reticular formation results in an increase in respiratory frequency. Thus, it is clear that excitation of the suprapontine system has a facilitatory influence on the brain-stem mechanism for breathing. There is much evidence (Cohen, 1964; Miller and Tenny, 1975) that the excitation of the suprapontine system is responsible for hypocapnic tachypnoea and hypoxic-induced tachypnoea in carotid-deafferented cats. It is quite possible that halothane-induced tachypnoea results from the same mechanism. In fact, all these different forms of tachypnoea have a common respiratory pattern: a decrease in tidal output and high frequency breathing. Recently, Tenny and Ou (1977) emphasized the importance of coupled influences from the cortex (inhibitory) and diencephalon (facilitatory) on the ponto-medullary centres. It is possible that halothane-induced tachypnoea is a result of removal of the inhibitory cortical influence by depressing the cortical activity selectively. However, it is also possible that halothane stimulates the diencephalon directly while depressing other areas.

ACKNOWLEDGEMENTS

We are grateful to Dr E. Mulligan for advice and discussion.

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MODIFICATIONS PAR L'HALOTHANE DE LA FONCTION RESPIRATOIRE CHEZ LE CHAT

RESUME

Des recherches ont été effectuées sur des chats légèrement anesthésiés en ce qui concerne l'effet de l'halothane sur la fonction respiratoire. A la suite de l'administration d'halothane à 2%, une augmentation passagère de la fréquence respiratoire s'est produite en raison du raccourcissement de la période d'expiration suivi d'une baisse progressive de la fréquence respiratoire due à la prolongation de l'inspiration; ceci a été démontré dans les deux cas, soit avant soit après la vagotomie. Au cours de l'état de calme dû à l'administration d'halothane à 0,5, 1,0 et 1,5%, et de la vagotomie, un écourtement de la période d'expiration et une augmentation progressive de la période d'inspiration ont été enregistrés. La fonction phrénique courante s'est abaissée progressivement à mesure que l'on augmentait la concentration de l'halothane. Ces résultats inclinent à penser que les modifications de la fonction respiratoire enregistrées au cours de l'anesthésie à l'halothane

risquent de mettre en jeu des mécanismes excitatoires centraux en dehors du système de la protubérance bulbaire.

HALOTHAN-INDUZIERTE ÄNDERUNGEN DES ATMUNGSBILDES BEI DER KATZE

ZUSAMMENFASSUNG

Die Wirkung von Halothan auf das Atmungsbild bei leicht anästhetisierten Katzen wurde untersucht. Bei 2% Halothan stellte sich eine vorubergehende Zunahme der Atmungsfrequenz infolge der Verkurzung der Atmungsdauer ein, mit anschliessender progressiver Abnahme der Atmungsfrequenz infolge der Verlängerung der Einatmung. Diese Ereignisse konnten sowohl vor als auch nach der Vagotomie vorgeführt werden. Während des stabilen Zustands, der sich bei 0,5, 1,0 und 1,5% Halothan und nach der Vagotomie einstellte, wurde eine Abnahme der Expirationsdauer und eine progressive Zunahme der Inspirationsdauer festgestellt. Die Zwerchfellminutenleistung nahm progressiv mit zunehmender Halothankonzentration ab. Diese Ergebnisse deuten an, dass die wahrend der Halothananästhesie beobachteten Änderungen des Atmungsbildes möglicherweise mit zentralen Reizmechanismen ausser dem Bulbopontinsystem zusammenhangen konnten.

CAMBIOS EN LA FUNCION RESPIRATORIA INDUCIDOS POR HALOTANO EN EL GATO

SUMARIO

Se averiguó el efecto del halotano sobre el contorno respiratorio de gatos ligeramente anestesiados. Luego de la administración de halotano al 2%, hubo un aumento pasagero de la frecuencia respiratoria a raíz de una disminución de la duración de expiración seguida por una reducción progresiva de la frecuencia respiratoria resultando de la prolongación de la inspiración; ambos cambios pudieron demostrarse antes y después de la vagotomía. Durante el estado estable obtenido después de la administración de halotano al 0,5 1,0 y 1,5% y de la vagotomía, se produjo un descenso de la duración de expiración, y un aumento progresivo de la duración de inspiración. El rendimiento frénico corriente bajó progresivamente a medida que se aumentaba la concentración de halotano. Estos resultados hacen pensar que los cambios de la función respiratoria vistos durante la anestesia por halotano pueden relacionarse con algunos mecanismos centrales excitatorios fuera del sistema de la protuberancia bulbar.

Br. J. Anaesth. (1980), 52, 1199

FAILURE OF NEOSTIGMINE TO PREVENT TUBOCURARINE NEUROMUSCULAR BLOCK IN THE ISOLATED ARM

S. A. Feldman and S. Agoston

SUMMARY

Neostigmine failed to modify the development of neuromuscular block in the presence of a high local concentration of tubocurarine. Only when the concentration of tubocurarine was reduced, and a suitable concentration gradient established between the receptor area and the plasma, did neostigmine increase the rate of recovery from the action of non-depolarizing neuromuscular blocking agents.

Baraka (1967) observed that neostigmine was unable to antagonize the neuromuscular block produced by tubocurarine if the plasma concentration of antagonist was greater than 2.0 μg ml^{-1} and caused only slow antagonism when the plasma concentration was greater than 1.0 μg ml^{-1} This effect was confirmed by Baraka in 1977. Katz and Katz (1975) described the relative ineffectiveness of agonist drugs to antagonize pancuronium block when the recovery of the indirectly elicited twitch was less than 20% of control unless a considerable time had elapsed since the administration of the last dose of pancuronium. This present study using the isolated arm technique (Feldman and Tyrrell, 1970) allowed us to study the effectiveness of various doses of neostigmine in antagonizing tubocurarine neuromuscular block both when the plasma drug concentration was high and when it was low.

METHOD

The "isolated arm" technique described by Feldman and Tyrrell in 1970 was used for these experiments. An arterial tourniquet was inflated on the upper arm to isolate it from the general circulation just before a dose of tubocurarine 2 mg diluted in 40 ml of saline was injected rapidly into a vein on the dorsum of the hand. The tourniquet was released at a set time after completion of the injection (tourniquet time). Neuromuscular conduction was monitored by stimulating the ulnar nerve at the wrist with a square-wave supramaximal stimulus of 0.2 ms at 0.5 Hz and recording the tension produced in the adductor pollucis muscles using a Statham UC3 load cell preloaded to 50 g.

In these experiments the dose of tubocurarine used was standardized at 2 mg, irrespective of the size of patient (52–82 kg), as the distribution volume was limited to one arm only.

Various doses of neostigmine were used to promote an increased agonist activity in these experiments. It was always mixed with atropine 1.2 mg to minimize muscarinic side-effects. When neostigmine was administered systemically the dose was standardized at 0.05 mg kg^{-1}, but when it was given in the isolated arm, doses from 0.25 to 1.5 mg in 40 ml of saline were used.

The original experiments were carried out on both conscious volunteers and patients anaesthetized with 1% halothane with nitrous oxide and oxygen before surgery, without any discernable difference in the results. However, in order to make our conclusions as clinically relevant as possible, only the results from the anaesthetized patients are included in this paper. The consent of patients to the procedure was obtained in all cases.

(1) In the control group of three patients, tubocurarine 2 mg diluted in 40 ml of saline was injected into the isolated arm and the tourniquet deflated after 2 min (fig. 1).

(2) Three experiments were carried out administering neostigmine and atropine systemically 5 min before the injection of the tubocurarine into the isolated arm (fig. 2A).

(3) Eight experiments were performed using mixtures of tubocurarine 2 mg and neostigmine 0.25 mg, 0.5 mg (fig. 2B), 1.0 mg or 1.5 mg together in the solution used in the isolated arm with a tourniquet time of 2 min. To control the

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0007-0912/80/121199-05 $01.00

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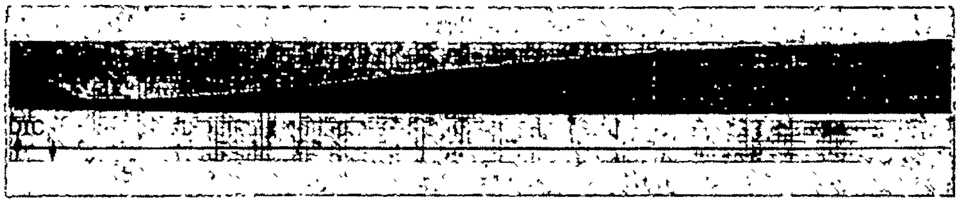

FIG. 1. Control injection of tubocurarine 2 mg in 40 ml of saline (↑DTC) in isolated arm. Tourniquet time 2 min. Recovery index (25 to 75% recovery time) = 13.5 min (the drug was injected as rapidly as possible immediately the tourniquet was inflated). ↓ = tourniquet release

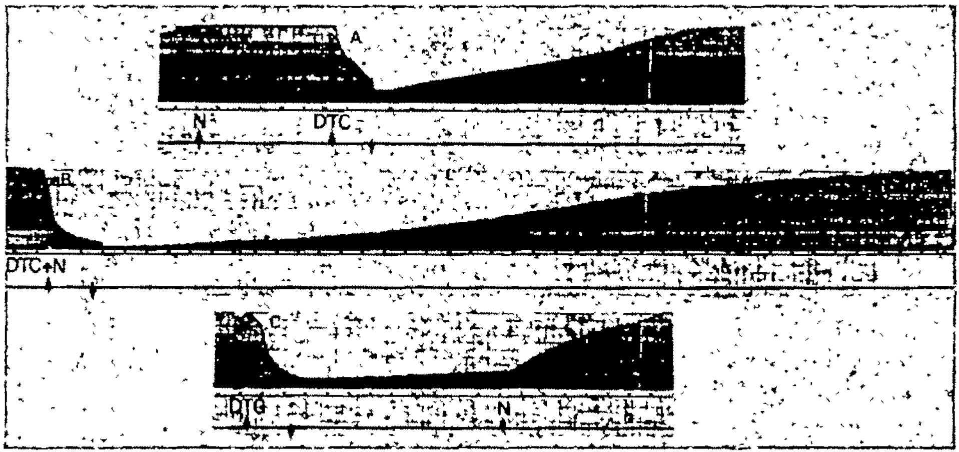

FIG. 2. A: Administration of neostigmine 0.05 mg kg^{-1} (↑N) 5 min before injection of tubocurarine (↑DTC) into the isolated arm. Tourniquet time 2 min. B: Neostigmine 0.5 mg and tubocurarine 2 mg (↑DTC+N) injected into the isolated arm. Tourniquet time 2 min. C: Administration of neostigmine 0.05 mg kg^{-1} (↑N) at 25% recovery of twitch height after block produced by tubocurarine 2 mg (↑DTC) in the isolated arm. Tourniquet time 2 min. ↓ = tourniquet release.

possible difference in onset time of neostigmine and tubocurarine, one additional experiment used a tourniquet time of 1 min and another experiment used a tourniquet time of 5 min.

(4) Following the establishment of neuromuscular block using tubocurarine 2 mg in the isolated arm with a 2-min, tourniquet time, four investigations were carried out administering neostigmine 0.05 mg kg^{-1}systemically at 25% recovery of neuromuscular transmission (fig. 2 C).

RESULTS

Amount of block

The extent of the neuromuscular block achieved in the isolated arm was not significantly altered by systemic pretreatment with neostigmine 0.05 mg kg^{-1} compared with control (table I: 92.7±9.2% block compared with 94.3±4.1). Mixing neostigmine 0.25 mg, 0.5 mg, 1.0 mg or 1.5 mg with tubocurarine 2 mg in the isolated arm produced 92.5±3.6% (table II) compared with control of 94.3±4.1% when tubocurarine was administered alone in the isolated arm. Reducing the tourniquet time to 1 min and increasing it to 5 min did not influence the amount of neuromuscular block produced (93.0±3.6% compared with control of 94.3±4.1%. Compared with the control group there was no statistically significant difference in the amount of block achieved in the three groups receiving neostigmine using the Mann–Whitney test for biological significance.

Recovery of neuromuscular transmission

The recovery index (Feldman, 1972)—the time taken for the twitch response to recover from 25% to 75% of its control height—was used to compare the recovery rates from the tubocurarine block in all the experiments. This gives a good comparative index of the rate of recovery of neuromuscular transmission.

TABLE I. *Effect of pretreatment with neostigmine 0.05 mg kg^{-1} on neuromuscular block produced by tubocurarine 2 mg*

	Max. block (%)	Time to 25% recovery (min)	Time to 75% recovery (min)	Time to full recovery (min)	Recovery index 25% to 75% (min)
Control	90	8	24	38	
	95	6	18.5	27	12.5
	98	8	21.5	32	13.5
Neostigmine	82	2.5	12.0	16.0	9.5
	98	15.0	26.5	36.0	11.5
	98	9.5	21.0	28.5	11.5

TABLE II. *Effect of neostigmine 0.5 mg injected concurrently with tubocurarine 2 mg or of neostigmine 0.05 mg kg^{-1} injected at 25% recovery, on the neuromuscular block produced by tubocurarine. * 1-min tourniquet time; † 5-min tourniquet time*

	Max. block (%)	Time to 25% recovery (min)	Time to 75% recovery (min)	Time to full recovery (min)	Recovery index 25% to 75% (min)	Mean
Neostigmine with tubocurarine 2 mg						
0.25 mg	90	2.0	14	>14	12	10.25
	95	4.0	12.5	22	8.5	
0.5 mg	94	6.0	17.5	<20	11.5	11.7
	85	2.6	14.5	18	11.9	
1.0 mg	92	4.0	16.5	24	12.5	12.25
	94	5.0	17.0	27	12.0	
1.5 mg	95	5.5	18.0	<25	12.5	12.55
	98	3.2	14.8	20	12.6	
0.5 mg*	92	5.0	18.5	27	13.5	
0.5 mg†	95	8.0	21.5	34	13.5	
Neostigmine at 25% recovery	—	—	—	—	5.6 2.5 4.2 6.5	

Compared with the control patients to whom no neostigmine was administered, patients receiving 0.05 mg kg^{-1} i.v. 5 min before tubocurarine 2 mg in the isolated arm demonstrated a quicker recovery of neuromuscular conduction (table I: 10.5 ± 1.73 min compared with 14.0 ± 1.8 min in the control). This is significantly more rapid (one-tailed Mann–Whitney test).

Adding neostigmine 0.25–1.5 mg with the 2 mg of tubocurarine had a small effect on the recovery index (table II compared with table I: 12.3 ± 1.7 min compared with 14.0 ± 1.8 min in control).

The administration of neostigmine 0.05 mg kg^{-1} at 20% recovery of neuromuscular block had a dramatic effect on reversal. The 25% to 75% recovery time was reduced to 4.7 ± 1.75 min compared with 14.0 ± 1.8 min recovery index in the control group (table II compared with table I).

DISCUSSION

The object of this investigation was to repeat *in vivo* experiments previously carried out by others to study agonist/antagonist relationships using *in vitro* preparations. As it was impossible to achieve similar equilibrium conditions in patients, the isolated arm technique was used to simulate *in vitro* conditions.

When tubocurarine 2 mg in 40 ml of saline is injected i.v. in the isolated arm, a concentration gradient of drug is achieved which results in sufficient drug passing to the receptor site to cause more than 90% neuromuscular block. By the end of the 2 min tourniquet time a state of "pseudo equilibrium" is established and, so long as the tourniquet is inflated, the block remains constant. The presence of this concentration of drug in the plasma determines the degree of neuromuscular block irrespective of the concentration of acetylcholine. The injection of neostigmine 0.25–1.5 mg with the tubocurarine in the isolated arm in these experiments must have increased the available acetylcholine at the receptor site, but failed to influence the amount of block produced by tubocurarine 2 mg. This is difficult to reconcile with *in vitro* experiments studying the interaction of agonist and antagonist agents at the neuromuscular junction, which have demonstrated consistent antagonism of the block. *In vitro*, larger doses of agonist are required to prevent neuromuscular block in the presence of greater concentrations of antagonist drug. This log-dose relationship has been demonstrated for a variety of agonist and antagonist drugs *in vitro* (Jenkinson, 1960; Lu, 1970; Waud, Cheng and Waud, 1973). However, if there are two factors controlling the recovery of neuromuscular transmission following the administration of an antagonist drug—the dissociation rate constant and the concentration gradient between receptor and blood—then, although increased acetylcholine production will facilitate the dissociation of the drug–receptor combination, the absence of a favourable concentration gradient will prevent the drug leaving the receptor area. As a result, the amount of block produced will be unaffected by the presence of neostigmine.

Once the tourniquet is released a favourable concentration gradient will be established and the effect of neostigmine in increasing the rate of drug–receptor dissociation will be revealed. This is most obvious at peak blood concentrations of neostigmine. The effect is most pronounced when the neostigmine is administered in high doses during recovery from neuromuscular block and less effective when administered in the same dose 5 min before the establishment of tubocurarine neuromuscular block. Even after the administration of small doses of neostigmine (0.25–1.5 mg mixed with tubocurarine), once the cuff was released and the blood concentration of tubocurarine reduced to subparalytic values, faster recovery was apparent in most patients although the mean was not significantly different from the mean control recovery index.

If one envisages a simple competition between acetylcholine and a non-depolarizing relaxant for receptor sites at the neuromuscular junction, then it should be possible to antagonize the action of a given concentration of antagonist in the biophase by suitably increasing the dose of agonist, provided sufficient time is allowed for equilibrium to be established. There have been several case reports indicating that even in the relatively stable pharmacokinetic conditions produced in anephric patients to whom a relative overdose of gallamine has been inadvertently administered, complete antagonism of the neuromuscular block by neostigmine is impossible (Fairley, 1950; Montgomery and Bennett-Jones, 1956; Feldman and Levi, 1963).

This is in agreement with Baraka's contention (1967, 1977) that the majority of cases of irreversible curarization are a result of high concentrations of drug in the plasma. Agoston, Feldman and Miller (1979) have suggested that, *in vivo*, the greater the diffusion gradient between the receptor site and the plasma, the more rapid will be the recovery from neuromuscular block. If the gradient is high (as in the isolated arm following release of the tourniquet) recovery is rapid. If the gradient is minimal (as after continuous infusion of antagonist) recovery is prolonged. This paper takes this concept one stage further by demonstrating the failure of neostigmine to prevent the development or modify the extent of the neuromuscular block produced by subparalytic concentrations of tubocurarine. This suggests that, unless a suitable gradient exists between the receptor and the plasma, allowing drug molecules to leave the receptor area once they have been displaced from the receptor site, it will be impossible to antagonize the neuromuscular block even by large doses of neostigmine.

ACKNOWLEDGEMENTS

We are indebted to Dr David Preston, Director of the Computer services at Westminster Hospital, for his help with the statistical analysis, and acknowledge the helpful suggestions of Professor W. C. Bowman and Dr Arnold Scaf in the preparation of this paper.

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LA NEOSTIGMINE N'EMPECHE PAS LE BLOCAGE NEUROMUSCULAIRE PAR LA TUBOCURARINE DANS LE BRAS ISOLE

RESUME

La néostigmine n'a pas été en mesure de modifier l'évolution du blocage neuromusculaire en présence d'une forte concentration locale de tubocurarine. Ce n'est que lorsque l'on réduisit la concentration de tubocurarine et que l'on établit un gradient de concentration approprié entre la zone réceptrice et le plasma que la néostigmine eut pour effet d'accroître le rythme de récupération contre l'action des agents non dépolarisants de blocage neuromusculaire.

NEOSTIGMINE NICHT FÄHIG, TUBOCURARIN-INDUZIERTE NEUROMUSKULÄRE BLOCKADE IM ISOLIERTENARM ZU VERHINDERN

ZUSAMMENFASSUNG

Neostigmine war nicht fähig, die Entwicklung einer neuromuskulären Blockade im Beisein einer hohen örtlichen Konzentration von Tubocurarin zu beeinflussen. Nur als die Konzentration von Tubocurarin reduziert und eine angemessene Konzentrationskurve zwischen Rezeptorbereich und Plasma erreicht wurde, konnte Neostigmine die Erholung von der Wirkung der nicht depolarisierenden neuromuskulären Blockierungsmittel beschleunigen.

LA NEOESTIGMINA NO LLEGA A PREVENIR EL BLOQUEO NEUROMUSCULAR POR LA TUBOCURARINA EN EL BRAZO AISLADO

SUMARIO

La neoestigmina no llegó a modificar el desarrollo del bloqueo neuromuscular frente a una alta concentración de tubocurarina. Sólo cuando se redujo la concentración de tubocurarina y se pudo establecer una gradiente adecuada de la concentración entre la zona receptora y el plasma, la neoestigmina aumentó el ritmo de recuperación a raíz de la acción de los agentes bloqueadores neuromusculares no-depolarizantes.

Br. J. Anaesth. (1980), **52**, 1205

EFFECT OF SINGLE ORAL DOSE OF PHENOBARBITONE ON LYMPHOCYTE BLASTOGENIC RESPONSE IN MAN

F. PUPPO, G. F. ADAMI, G. CORSINI, G. M. ZAVARISE AND J. ZATTONI

SUMMARY

A single oral dose of phenobarbitone 1.5 mg kg^{-1} was given to 18 normal subjects to evaluate the effects on lymphocyte function. Serum barbiturate concentrations and lymphocyte blastogenic response to three mitogens (PHA, Con A, PWM) were tested before and at 2, 12 and 36 h after drug administration. A serum barbiturate plateau of about 2 μg ml^{-1} was maintained from 2 to 36 h. Lymphocyte blastogenesis was reduced with barbiturate compared with controls. However, the reduction was significant only at 36 h ($P<0.01$).

Lymphocyte response to non-specific mitogens, T and B lymphocyte counts and cutaneous delayed hypersensitivity to antigens, have been found to decrease to a variable extent in the first few days following surgery (Cullen and Van Belle, 1975; Slade et al., 1975; Miller et al., 1976; Roth et al., 1976; Tarpley et al., 1977; Sochat, Miller and Snyder, 1979). Surgical stress and anaesthetic drugs have been suggested as likely factors in postoperative immunosuppression (Bruce and Wingard, 1971; Howard and Simmons, 1974; Roth et al., 1976; Tarpley et al., 1977; Sochat, Miller and Snyder, 1979; Walton, 1979).

In a previous study, the *in vitro* lymphocyte blastogenic response was found to decrease slightly during the 3 days preceding surgery (Adami et al., 1980). An impending operation is a stressing condition and may be a possible cause. However, such an effect might be a result of phenobarbitone, usually given to our patients as hypnotic. This study was undertaken since the few published reports do not agree on the immunosuppressive action of barbiturates (Park and Brody, 1971; Gabourel, Davies and Rittenberg, 1977).

METHODS

Eighteen normal volunteers (nine male), aged 21–58 yr and who were not taking drugs, were studied. Each subject received a single oral dose of phenobarbitone 1.5 mg kg^{-1} at 8 p.m.

At 8.00 a.m., before administration of barbiturate (−12 h), venous blood samples were taken for measurement of serum barbiturate concentration and lymphocyte blastogenic response. Measurements were repeated 2, 12 and 36 h after drug administration, but no lymphocyte cultures were made at 2 h.

Venous blood was drawn into 10-ml disposable syringes coated with preservative-free heparin 10 u. ml^{-1} (Calbiochem, La Jolla, USA). Lymphocytes were collected after centrifugation at 400 *g* for 20 min through a Ficoll–Urovison gradient (sp.gr.t. 1077) and washed three times in Hanks balanced salt solution (Eurobio, Labtek, Paris). Cells were resuspended at a concentration of 2×10^6 ml^{-1} in TC 199 medium buffered with Hepes and 7% bicarbonate (Eurobio, Labtek, Paris), supplemented with 1% 1-glutamine, penicillin 100 i.u. ml^{-1}, streptomycin 100 μg ml^{-1} and 20% heat-inactivated autologous plasma. Cultures were performed in microtitre plates with U-bottomed wells (Linbro, Hamden, USA). One hundred microlitre of the cell suspension was added to each well with 100 μlitre of solution containing TC 199 (control cultures), phytohaemagglutinin 100 μg ml^{-1} (PHA, Wellcome), concanavalin A 100 μg ml^{-1} (Con A, Pharmacia AB, Upsala) or pokeweed mitogen (PWM, Grand Island Biological Co., New York) diluted 1 : 20. The same batches of mitogens were used for the entire study. Cultures were performed in triplicate and plates incubated at 37 °C in a humidified atmosphere for 55 h. Methyl-^{3}H-thymidine 0.5 μCi (specific activity 2 Ci mmol^{-1}, Amersham,

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0007-0912/80/121205-03 $01.00

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TABLE I. *Lymphocyte blastogenic response. Mean ± SD (expressed as c.p.m.) to PHA, Con A and PWM mitogens.** Significance of variance analysis at 0.01 level;* n = *number of subjects*

	Time (h)		
Mitogen	−12	12	36
PHA ($n = 18$)	39 066 ± 8854	37 768 ± 11 452	27 564 ± 12 778**
Con A ($n = 18$)	16 843 ± 9303	16 560 ± 12 438	8709 ± 5115**
PWM ($n = 18$)	22 619 ± 7749	21 649 ± 8007	15 962 ± 7630**

England) were added to each well. Seventeen hours later, cultures were harvested on to glass fibre filters with a semiautomatic device (Sacrificator, Labtek). Filters were added to 2.5 ml of scintillation fluid and counted in an LKB scintillation spectrometer. Blastogenic response was expressed as counts per min (c.p.m.). Our normal laboratory ranges are: 29 000–56 000; 14 000–33 000 and 7000–31 000 c.p.m. respectively for PHA, Con A and PWM stimulation.

Gas–liquid chromatography was used for measurement of serum phenobarbitone concentration (Kupferberg, 1970).

Analysis of variance was performed between c.p.m. values and between serum barbiturate concentrations at the times sampled.

RESULTS

Serum barbiturate concentrations. Values at −12, 2, 12 and 36 h were, respectively: 0, 1.95 ± 0.53 $\mu g\ ml^{-1}$, 1.96 ± 0.39 $\mu g\ ml^{-1}$ and 2.01 ± 0.66 $\mu g\ ml^{-1}$. There was no significant difference between 2, 12 and 36 h.

Lymphocyte blastogenesis (table I). Basal c.p.m. values of all subjects were in the normal range for the three mitogens. From −12 to 12 h, c.p.m. decreased, but not significantly. Significant decreases in c.p.m. were found between −12 and 36 h and between 12 h and 36 h ($P < 0.01$ for all mitogens tested). Mean c.p.m. percent decreases at 36 h showed no differences between mitogens.

DISCUSSION

Oral administration of a single dose of phenobarbitone 1.5 $mg\ kg^{-1}$ resulted in serum concentrations of about 2 $\mu g\ ml^{-1}$. This value was achieved 2 h after drug intake and maintained 36 h, so that the serum concentration of phenobarbitone was assumed to be constant for the period of study (Buchtal and Svensmark, 1971). Mean lymphocyte blastogenic response to three different mitogens (PHA, Con A and PWM) was reduced in the presence of barbiturate compared with control values, the effect increasing with time. However, the mean decrease was significant only at 36 h. The changes were the same with the different mitogens used.

Our data suggest that phenobarbitone has an immunosuppressive action and this can follow a single oral hypnotic dose which results in low serum drug concentrations compared with values required for control of epilepsy (Svensmark and Buchtal, 1963). However, the serum concentrations achieved in this study are similar to that used in lymphocyte cultures by Park and Brody (1971) which was associated with a significant decrease in DNA synthesis under PHA stimulation.

There is a latency of 12 h or more in the *in vivo* appearance of phenobarbitone immunosuppression. This delay may represent the time required to inhibit the biosynthetic pathway leading to DNA synthesis (Park and Brody, 1971). Immunosuppression observed before operation in surgical patients (Adami et al., 1980) can be attributed to phenobarbitone only in the few patients receiving this hypnotic two or three nights before surgery.

ACKNOWLEDGEMENTS

The authors are grateful to Miss G. Besio (Department of Neurology, University of Genova, Italy) for serum barbiturate concentration determinations and to Dr E. Traverso (Cattedra di Patologia Chirurgica "R", University of Genova, Italy), Miss S. Lenzi and Miss R. Pattarini (Cattedra di Patologia Medica "R", University of Genova, Italy) for technical assistance.

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EFFET D'UNE DOSE ORALE UNIQUE DE PHENOBARBITONE SUR LA REPONSE BLASTOGENIQUE DES LYMPHOCYTES CHEZ L'HOMME

RESUME

On administra à 18 sujets normaux une dose orale unique de phénobarbitone de 1,5 mg kg^{-1} pour en évaluer les effets sur la fonction lymphocytaire. Des essais portant sur des concentrations de barbituriques dans le sérum et sur la réponse blastogénique des lymphocytes *vis-à-vis* de trois mitogènes (PHA, Con A, PWA) ont été effectués avant l'administration de la substance et 2, 12 et 36 h après celle-ci. Un palier d'environ 2 µg ml^{-1} de barbiturique de sérum se maintint de 2 à 36 h. La blastogénèse lymphocytaire diminua sous l'effet du barbiturique en comparaison avec les contrôles. Toutefois, cette diminution ne devint significative qu'après 36 h ($P<0{,}01$)

WIRKUNG EINER EINZELNEN MÜNDLICHEN DOSIS VON PHENOBARBITON AUF DIE LYMPHOZYTBLASTOGENISCHE REAKTION BEIM MENSCHEN

ZUSAMMENFASSUNG

Eine einzelne mündliche Dosis von Phenobarbiton 1,5 mg kg^{-1} wurde bei 18 normalen Versuchspersonen verabreicht, um die Wirkung auf die Lymphozytfunktion auszuwerten. Serumbarbiturkonzentrationen und die lymphozytblastogenische Reaktion auf 3 Mitogene (PHA, Con A, PWM) wurden vor und 2, 12 und 36 Stunden nach Verabreichung getestet. Eine Serumbarbiturplateau von ca. 2 µg ml^{-1} wurde von 2 bis 36 Stunden aufrechterhalten. Die Lymphozytblastogenese wurde mit Barbiturpräparaten im Vergleich zu Kontrollen reduziert. Die Reduktion war jedoch nur bei 36 Stunden bedeutend ($P<0{,}01$).

EFECTO DE UNA DOSIS ORAL UNICA DE FENOBARBITONA EN LA RESPUESTA BLASTOGENICA DE LOS LINFOCITOS EN EL HOMBRE

SUMARIO

Se administró una dosis oral única de fenobarbitona de 1,5 mg kg^{-1} a 18 sujetos normales a fin de evaluar los efectos sobre la función de los linfocitos. Se llevaron a cabo ensayos con concentraciones de barbituratos en el suero y la respuesta blastogénica de los linfocitos a tres mitógenos (PHA, Con A, PWM) antes y 2 h, 12 y 36 h después de la administración de la substancia. Se mantuvo una plataforma de barbiturato en el suero de alrededor de 2 µg ml^{-1} de 2 a 36 h. La blastogénesis de los linfocitos se redujo con el barbiturato en comparación con los controles. Sin embargo, la reducción llegó a ser significante a las 36 h solamente ($P<0{,}01$).

Br. J. Anaesth. (1980), 52, 1209

FAZADINIUM AND PANCURONIUM: A PHARMACODYNAMIC STUDY*

C. J. HULL, M. J. M. ENGLISH AND A. SIBBALD

SUMMARY

The neuromuscular blocking characteristics of fazadinium and pancuronium were compared using a general pharmacodynamic model. Since it characterizes the overall relationship between dose and effect, the model can be used to determine precisely equipotent doses, compare time–effect curves, and reconcile the apparently inconsistent clinical and pharmacokinetic characteristics of the two drugs. Fazadinium was shown to have a shorter duration than pancuronium, and appeared to exhibit less variation between subjects. The potency ratio varied between 3.4 : 1 and 7.2 : 1, depending upon the definition chosen. A general solution for the three-compartment open mammillary model, following any set of initial conditions is presented as an appendix. These equations allow explicit computation of any pattern of drug incrementation into any compartment of the model.

In small mammals, fazadinium is a non-depolarizing neuromuscular blocking agent with short latency and a very brief duration of action (Brittain and Tyers, 1973). It also produces a dose-dependent increase in heart-rate, because of a combination of vagal and ganglionic blockade (Marshall, 1973).

In man, fazadinium has a short latency (Blackburn and Morgan, 1978), but a more prolonged duration of action which has been compared to that of pancuronium (Simpson et al., 1972; Kean, 1975). Therefore it might be expected that fazadinium would exhibit pharmacokinetic behaviour similar to that of pancuronium. Surprisingly, Duvaldestin and others (1978) showed that, while fazadinium could be characterized by a two-compartment open model and appeared to have a similar volume of distribution, it was much more rapidly eliminated, with a clearance twice that of pancuronium. Tyers (1978), using a bioassay technique, claimed that fazadinium had a plasma clearance half-time of only 1 min, and that, as suggested by Hashimoto and colleagues (1979), the rate-limiting step for the termination of effect is most likely to be the rate of drug receptor dissociation.

These studies suggest that fazadinium and pancuronium may exhibit different concentration–response relationships at receptor level. This hypothesis may be tested by comparing pharmacodynamic models of both drugs.

Following the principles set out by Furchgott 1955) and Wagner (1971), it was shown (Van Beem et al., 1977; Hull et al., 1978) that pancuronium concentrations in a hypothetical "biophase" compartment can be derived by simultaneous consideration of plasma concentration and measured effect (twitch depression). These communications assumed a linear relationship between log-concentration and effect in order to construct a simple pharmacodynamic model. However, this was only valid for values of twitch depression between 20 and 80%.

In the present study, a log-logistic function (logit effect *v.* log concentration) (Wagner, 1968) is used to relate effect with concentration, following Sheiner and colleagues (1979) who used our "negligible biophase" concept to construct a full-range model for tubocurarine.

Simultaneous consideration of models for both drugs might be expected to demonstrate a rationale for the apparently inconsistent behaviour reported by other authors.

METHOD

Fazadinium

Five healthy adults about to undergo operations on the body surface consented to take part in the investigation. Each was premedicated with morphine and hyoscine 1 h before induction.

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*A detailed account of the pharmacokinetic symbols used in this paper may be found in a recent editorial (Hull, 1979a). See also Hull (1979b) and Norman (1979).

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0007–0912/80/121209–13 $01 00

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Anaesthesia was induced with thiopentone and fentanyl, the larynx was sprayed with topical lignocaine (10%), and an endotracheal tube was passed. Ventilation of the lungs was controlled throughout, using 65% nitrous oxide in oxygen and end-tidal PA_{CO_2} was maintained in the range 5.07–5.60 kPa (38–42 mm Hg). Endotracheal carbon dioxide concentrations were measured using a Beckman LB2 infra-red analyser, calibrated for carbon dioxide in 65% nitrous oxide. Increments of fentanyl were administered i.v. as required to allow controlled ventilation.

Using subcutaneous needle electrodes, the left ulnar nerve was stimulated 1 cm above the ulnar styloid by rectangular, supramaximal, 200-μs pulses at a frequency of 0.2 Hz, delivered by a Grass S44 stimulator with stimulus isolation unit. The hand was immobilized, and the tension in the adductor pollicis muscle measured by a Statham "Gold cell" transducer with load attachment. Signals from the transducer were conditioned by a peak-height analyser with automatic zero correction, and recorded on magnetic tape (SE Labs 8/4). After a period of stabilization (> 10 min) a bolus dose of fazadinium 0.46–0.8 mg kg^{-1} was given i.v., and serial 5-ml blood samples were drawn from a central venous catheter at 1, 3, 5, 7, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100 and 120 min after injection. The plasma was separated from each sample after centrifugation, and stored at −15 °C until assay.

Plasma fazadinium concentrations were estimated in duplicate by a modification of Pastorino's fluorimetric technique (Pastorino, 1978; Oyston, 1979). The method is based upon the conversion of fazadinium to 3-methyl-2-phenyl-imidazo-(1, 2a)-pyridine, which can be estimated directly by spectrofluorimetry, and differs from the original by performing the stage of alkaline hydrolysis at 37 °C, instead of 50 °C. The coefficient of variation for the assay was 6.4%, the sensitivity 0.0130 μg ml^{-1}, and the goodness of fit to a straight line (r^2) 0.9977. In order to minimize errors, twitch height values were recovered directly from the magnetic tape record by a logging voltmeter (SE Labs 212) under the control of a programmable calculator (H.P. 9815A), and transferred to punched tape for storage and subsequent analysis.

Compartmental analysis

In each case, an optimal biexponential decay function of the form

$$C_t = A.e^{-\alpha t} + B.e^{-\beta t} \tag{1}$$

was fitted to the duplicate mean fazadinium concentrations by the method of maximum likelihood (Holland, 1976), and the parameters of the corresponding two-compartment open model calculated (table I).

TABLE I. *Pharmacokinetic data for five patients given fazadinium.* $T_{\frac{1}{2}}^{\alpha}$ *and* $T_{\frac{1}{2}}^{\beta}$ *are half-times for the* α *and* β *phases of the biexponential decay function which was fitted to serial plasma concentrations* ($T_{\frac{1}{2}}^{\alpha} = \ln 2/\alpha$). V_1, V_2, *etc. are the parameters of a corresponding two-compartment open model*

	Patient				
	A	B	C	D	E
Age (yr)	54	61	45	63	22
Weight (kg)	75	54	65	59	53
Dose (mg)	60	30	30	45	30
$T_{\frac{1}{2}}^{\alpha}$ (min)	1.96	1.48	3.84	1.64	1.68
$T_{\frac{1}{2}}^{\beta}$ (min)	20.44	53.43	48.80	39.23	48.03
V_1 (litre)	3.86	2.05	5.85	3.11	2.59
V_2 (litre)	5.88	8.73	8.08	8.01	8.78
k_{12} (h^{-1})	10.10	18.46	5.40	15.88	16.39
k_{21} (h^{-1})	6.64	4.56	3.91	6.18	4.85
k_{10} (h^{-1})	6.50	4.78	2.36	4.35	4.43

Comparison between concentration and effect

From the time at which each twitch response was measured, the corresponding plasma concentration was estimated by solving the appropriate biexponential decay function (equation (1)) for that time. By considering serial values during both onset and offset of effect, it was possible to construct a concentration–response plot for each subject.

In each case, the plot showed that, for a specified degree neuromuscular block, there was a wide discrepancy between the concentrations found during onset and offset. A concentration–response plot for the peripheral (V_2) compartment of the kinetic model showed a similar discrepancy. Since the degree of neuromuscular block should be functionally related to drug concentration (Waud, 1968), it is concluded that the site of action, or biophase, cannot be identified with either compartment of the model. In this respect fazadinium is similar to pancuronium (Hull et al., 1978) and tubocurarine (Sheiner et al., 1979).

It follows that the biophase (now designated compartment 3) must be considered as a separate entity. If the biophase volume (V_3) is assumed to be negligibly small, the appropriate compartmental rate constants can be estimated by the following procedure (Hull et al., 1978):

Estimation of biophase rate constants

(i) Times t_a and t_b are determined, at which twitch tension was 70% depressed during onset and offset respectively.

(ii) k_{31} is assigned an arbitrary value, and since V_3 is very small, k_{13} can be assumed to be negligible also ($k_{13} = V_3 . k_{31}/V_1$).

(iii) For the given dose, and the previously determined volumes and rate constants, the constants and exponents of the expression

$$C_3 = L.e^{-\alpha t}+M.e^{-\beta t}+N.e^{-\gamma t} \qquad (2)$$

are determined (see appendix). Thus, for any time t, the concentration in the biophase can be calculated.

(iv) Equation (2) is solved for t_a and t_b. If $C_3{}^a = C_3{}^b$, the estimated value of k_{31} is accepted; if not, it is modified and the procedure repeated from (iii). By successive approximation, the optimal value for k_{31} is determined (table III). When V_3 is negligible, $\gamma = k_{31}$, and the biophase half-life can be designated $T_{\frac{1}{2}}{}^{\gamma}$, and calculated from

$$T_{\frac{1}{2}}{}^{\gamma} = \ln 2/k_{31}.$$

Calculation of biophase drug concentrations

For serial values of t, equations (1) and (2) can now be solved to yield simultaneous values of C_1 and C_3. It can be seen from figure 1 that drug log-concentration in the biophase increases to a maximum after several (6.37±0.28) min, and then decreases at the same rate as that in plasma.

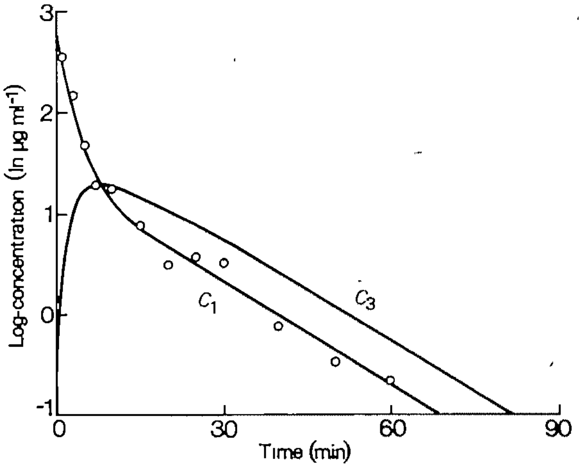

FIG. 1. Measured plasma log-concentrations of fazadinium in patient A, following a bolus dose of fazadinium 60 mg. A biexponential function (C_1) is fitted to the values of concentration, and characterizes the time-course of drug concentration in the central compartment (V_1) of a two-compartment open model. The three-exponential function (C_3) describes the time-course of apparent concentration in the biophase (V_3).

By taking values of twitch suppression during both onset and offset, and solving equation (2) for the times at which they occurred, a biophase concentration–effect plot may be constructed. The plots for all five subjects were sigmoid, and exhibited minimal hysteresis (fig. 2).

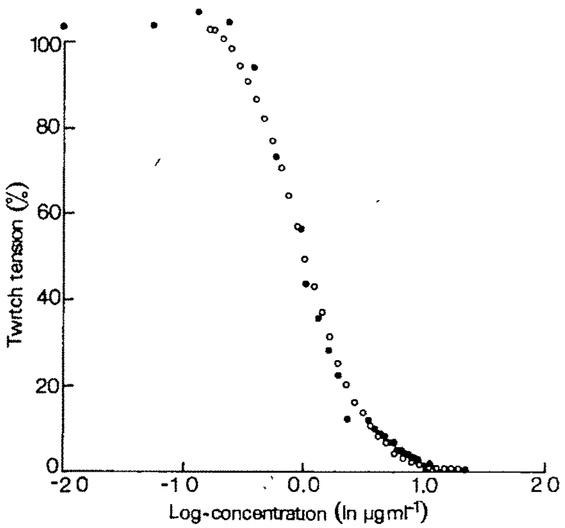

FIG. 2. Measured twitch tension (percentage of control) plotted against computed log-concentrations in the biophase for patient A (that is, function C_3 in figure 1). The co-ordinates plotted during both onset (●) and offset (○) of effect conform to a single sigmoid curve.

Pancuronium

The twitch response and concentration data from a previous study of pancuronium (Hull et al., 1978) were re-processed by the computer programs used for fazadinium, in order to ensure comparability (table II).

TABLE II. *Pharmacokinetic data for five patients given pancuronium*

	Patient				
	a	b	c	d	e
Age (yr)	65	33	63	50	27
Weight (kg)	61	54	66	82	71
Dose (mg)	4	4	4	4	4
$T_{\frac{1}{2}}{}^{\alpha}$ (min)	6.11	9.65	3.38	4.36	2.41
$T_{\frac{1}{2}}{}^{\beta}$ (min)	112.4	83.18	122.32	94.46	88.49
V_1 (litre)	3.8	5.0	3.4	3.9	3.4
V_2 (litre)	3.7	5.1	4.6	6.1	4.9
k_{12} (h^{-1})	3.16	1.82	6.78	5.35	9.79
k_{21} (h^{-1})	3.24	1.78	5.01	3.42	6.79
k_{10} (h^{-1})	0.77	1.20	0.83	1.23	1.18

The computed distribution volumes and clearances differ from those in the original communication, since here they are calculated from "total" (instead of "free") concentrations.

In this study the stimulus repetition frequency was 0.08 Hz, thus differing from that used in the fazadinium series (0.2 Hz). In view of recent evidence (Ali and Savarese, 1980), it was considered unlikely that the responses to these low frequencies would differ significantly.

Linear transformation of concentration–effect curve

Following Ariens and Simonis' (1964) observation that, in isolated organ preparations, plots of log effect/(1 – effect) against log concentration (Hill plots) were linear over a very wide range, the biophase concentration–effect plots for both pancuronium and fazadinium were redrawn in this form (fig. 3).

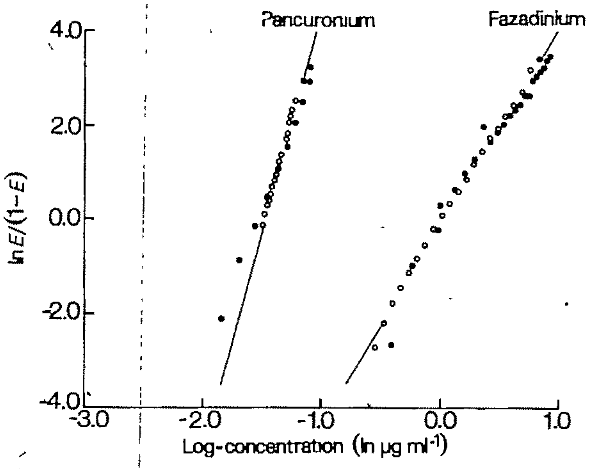

FIG. 3. ln $[E/(1-E)]$ (E = fractional effect) plotted against computed biophase log-concentrations for patient A (fazadinium) and patient d (pancuronium). This construction is also known as a Hill plot. From the values of log-concentration when ln $[E/(1-E)] = 0$, the concentrations at 50% effect (EC_{50}) are readily determined for each drug. ● = onset; ○ = offset.

Since the logit function ln $[E/(1-E)]$ is sensitive to imprecision at the extremes of effect, values outside the logit range ±3.48 (3–97% effect) were discarded.

Although there is some variation, the plots do not deviate greatly from linearity, so that straight lines can be fitted to the *offset* values by the method of least squares ($r^2 > 0.867$ in all cases). Since the onset values are greatly affected by small variations in k_{31}, they are excluded from the regression. Each straight line expresses an estimate of the relationship between concentration and effect for that subject, and is characterized by the gradient (s) and ordinal intercept (ln.a). The concentrations corresponding to 50% effect (when ln $[E/(1-E)] = 0$) can be calculated ($EC_{50} = a^{-1/s}$), and are shown with values s in table III.

TABLE III. *Biophase rate constants* (k_{31}), *Hill plot slopes* (s), *and* EC_{50} *for all subjects. The values for* s *and* EC_{50} *for each subject can be used to solve equation* (5)

	Patient	k_{31} (h^{-1})	s	EC_{50} (µg ml^{-1})
Fazadinium	A	6.77	4.25	1.043
	B	5.84	4.68	1.002
	C	13.62	5.32	0.909
	D	9.49	3.91	1.047
	E	7.43	4.16	1.025
Pancuronium	a	13.04	4.96	0.349
	b	12.31	5.37	0.229
	c	8.46	6.83	0.293
	d	10.86	9.23	0.230
	e	18.87	11.38	0.376

THE PHARMACODYNAMIC MODEL

The Hill plots in figure 3 are a graphic representation of the log-logistic function:

$$\ln\frac{E}{1-E} = s\ln C + \ln . a \tag{3}$$

where E = fractional effect and $a = E/(1-E)$ when $\ln . C = 0$.

This can be expressed in exponential form:

$$\frac{E}{1-E} = (C)^s . a \tag{4}$$

With a expressed in terms of EC_{50}, equation (4) can be rearranged to solve for E:

$$E = \frac{(C)^s}{(EC_{50})^s + (C)^s} \tag{5}$$

Since values of s and EC_{50} have been determined for each subject, this function (Wagner, 1968) can now be used to determine the likely degree of twitch depression for any biophase drug concentration.

Equation (5) thus completes a pharmacodynamic model (fig. 4) which, assuming linear kinetics, can estimate the expected pharmacological response to any dose or doses of the appropriate drug within the timespan of the original

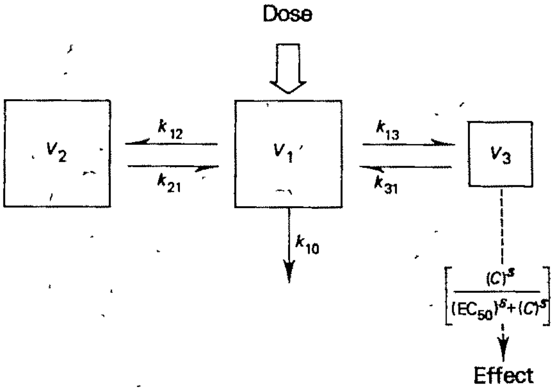

FIG. 4. The general pharmacodynamic model. By reference to tables I–III, a full-range model for each subject can be constructed, and solved for any dose or doses of drugs (see Appendix).

observations, given any specified set of initial concentrations in the three compartments. This has become possible with the development of a general solution to the three-compartment open mammillary model. The Appendix contains a detailed account of the mathematical method.

Comparison of fazadinium and pancuronium

It is clear that, in some respects fazadinium and pancuronium behave similarly. The recovery rates are comparable (table IV), but since onset and recovery times are dose-dependent, it is not possible to draw any direct conclusions as to similarity.

TABLE IV. *Onset and recovery of twitch response following single doses of fazadinium and pancuronium (mean ± SEM)*

	Fazadinium	Pancuronium
Onset time to 10% of control (min)	1.80 ± 0.15	3.44 ± 0.72
Recovery time to 50% of control (min)	54.68 ± 3.43	51.36 ± 8.02
Recovery rate at 50% of control (% min^{-1})	2.07 ± 0.38	2.32 ± 0.41

Both drugs are initially distributed into small volumes, and redistribute rapidly, so that the mean values of V_1 and $T_{\frac{1}{2}}^{\alpha}$ do not differ significantly (table V).

However, other aspects of disposition and activity show significant differences. Since V_2 for fazadinium is larger than that for pancuronium, it may be expected that, at the end of the distributive (α) phase, a smaller proportion of the dose will remain in the central compartment. This effect will be accentuated by the significantly larger value of k_{12} ($P = 0.022$) for fazadinium, so that it will not only be distributed further, but also more rapidly. Fazadinium is also eliminated much more rapidly, so that k_{10}, clearance and terminal half-life are all highly significantly greater than for pancuronium.

Pharmacodynamic factors also show differences. The gradient of the Hill plot (s) is significantly greater ($P<0.05$), and the concentration for 50% effect (EC_{50}) significantly smaller ($P<0.01$) for pancuronium than for fazadinium.

TABLE V. *Comparison of fazadinium and pancuronium models by statistical analysis of data from tables I, II and III. P is the probability that the means (± SEM) do not differ. In the cases of* P *values marked* the variances differed significantly* (F *ratio test*), *and the means were compared using Wilcoxon's rank-sum test. All other means were compared using Student's* t *test*

	Fazadinium	Pancuronium	P
Age (yr)	49.00 ± 7.47	47.60 ± 7.69	<0.1
Weight (kg)	61.20 ± 4.07	66.90 ± 4.74	<0.1
V_1 (litre)	3.49 ± 0.66	3.90 ± 0.30	<0.1
V_2 (litre)	7.90 ± 0.53	4.88 ± 0.39	0.002
V^{ss} (litre)	11.39 ± 0.69	8.78 ± 0.53	0.018
k_{12} (h^{-1})	13.25 ± 2.40	5.38 ± 1.40	0.022
k_{10} (h^{-1})	4.49 ± 0.66	1.04 ± 0.10	<0.01*
k_{31} (h^{-1})	8.63 ± 1.39	12.71 ± 1.73	<0.1
Cl (litre h^{-1})	14.66 ± 2.29	4.11 ± 0.60	<0.01*
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.12 ± 0.44	5.18 ± 1.27	0.05*
$T_{\frac{1}{2}}^{\beta}$ (min)	41.99 ± 5.85	100.17 ± 7.41	<0.001
$T_{\frac{1}{2}}^{\gamma}$ (min)	5.26 ± 0.71	3.50 ± 0.44	0.008
s	4.46 ± 0.25	7.75 ± 1.21	<0.05*
EC_{50} (μg ml^{-1})	1.005 ± 0.025	0.296 ± 0.030	<0.001

Comparison of potencies

If the values of EC_{50} are compared (table VI), an apparent potency ratio of 3.40 : 1 is obtained. Since this does not give the clinician any useful guide to dose requirement, the doses required to

TABLE VI. *The comparative potencies of fazadinium and pancuronium, determined by solution of the pharmacodynamic models of both drugs (mean ± SEM)*

	Fazadinium	Pancuronium	Ratio
EC_{50} (μg ml^{-1})	1.005 ± 0.025	0.296 ± 0.030	3.40 : 1
ED_{50} (mg)	12.63 ± 0.96	2.111 ± 0.142	5.98 : 1
ED_{90} (mg)	20.84 ± 1.80	2.907 ± 0.18	7.18 : 1

produce 50% (ED_{50}) and 90% (ED_{90}) block were calculated for each model. The potency ratio for ED_{50} was 5.98 : 1, and for ED_{90}, 7.18 : 1.

Comparison of predicted recovery times following standardized doses

In order to compare the durations of effect of two drugs, it is essential that equipotent doses are given. Since it has been shown that the potency ratio differs between EC_{50}, ED_{50} and ED_{90}, the last was chosen as a comparator, since it corresponds (approximately) to a minimal effective clinical dose. The duration of effect was taken as the predicted recovery time to 50% of control twitch tension following a single bolus dose. Each model was computed for $ED_{90} \times 1, 2, 3$ and 4. The recovery times for both drugs are compared in table VII. It is evident that, for a minimal effective dose (ED_{90}), both drugs exhibit similar durations of effect.

TABLE VII. *Predicted recovery times for all models, following standardized "doses" of fazadinium or pancuronium (expressed as the mean duration (min ± SEM) of the time taken to recover to 50% of control). P indicates the probability that the means do not differ, calculated by Student's* t *test or *Wilcoxon's rank-sum test*

Dose ($\times ED_{90}$)	Fazadinium	Pancuronium	*P*
1	26.6 ± 2.5	26.5 ± 5.7	>0.1
2	63.1 ± 7.2	104.1 ± 19.5	>0.05*
3	87.6 ± 9.8	161.6 ± 24.3	0.022
4	105.0 ± 12.0	203.1 ± 27.4	0.012

When the dose is increased to $2 \times ED_{90}$, the recovery times show considerable variation. In some cases, the pancuronium model predicts a greatly increased duration of effect, but there is some overlap with the fazadinium results so that the difference between the means, although large, is not significant. At three and four times the original dose, the pancuronium model predicts a

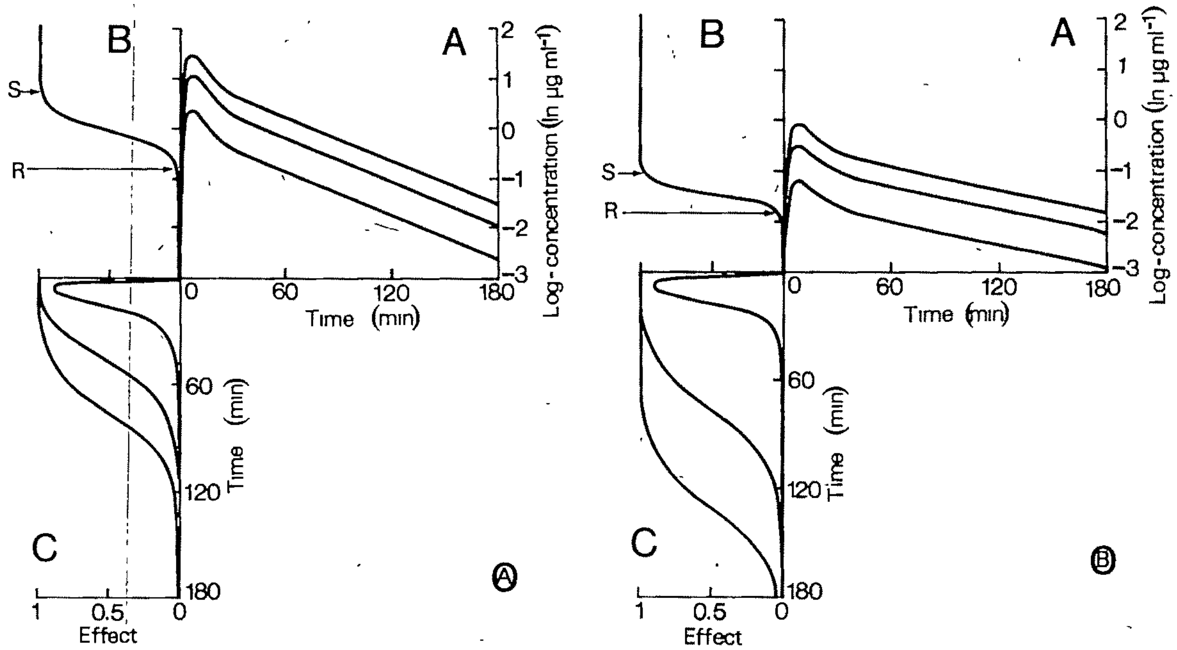

FIG. 5. Dose–effect diagrams for individual models. Ⓐ: Fazadium (patient C); Ⓑ: Pancuronium (patient d). The three-quadrant diagrams illustrate the influence of biophase log-concentrations following bolus doses of $ED_{90} \times 1, 2$ and 3 (quadrant A) and the sigmoid relationship between log-concentration and effect (quadrant B) on the time-effect curves (quadrant C). Points "R" and "S" indicate the log-concentrations corresponding to 2% and 98% effect respectively. It is clear that the range of concentrations (the pharmacodynamic zone) between "R" and "S" is appreciably narrower in the pancuronium model. Ⓐ. A = biophase fazadinium concentrations following $ED_{90} \times 1$, 2 and 3; $ED_{90} = 16.20$ mg; $T_{\frac{1}{2}}{}^{\beta} = 48.8$ min. B = concentration–response curve; $EC_{50} = 0.909$ µg ml^{-1}, $s = 5.32$. C = effect-time curves. Recovery to 90% occurs at 17.5, 49, and 77 min. Ⓑ. A = biophase pancuronium concentrations following $ED_{90} \times 1$, 2 and 3; $ED_{90} = 2.322$ mg; $T_{\frac{1}{2}}{}^{\beta} = 94.46$ min. B = concentration–response curve; $EC_{50} = 0.23$ µg ml^{-1}; $s = 9.23$. C = effect–time curves. Recovery to 90% occurs at 18, 77 and 132 min.

larger increase in duration than that for fazadinium, so that $P = 0.022$ for $ED_{90} \times 3$, and $P = 0.012$ for $ED_{90} \times 4$.

Comparison of predicted dose–effect curves

Figure 5 shows time–effect curves for a range of doses, constructed from a representative model in each group. The three-quadrant diagrams show that each time–effect curve (quadrant C) is dependent not only on biophase concentration (quadrant A), but also on the concentration–effect characteristic (quadrant B).

The predicted 50% recovery times following increasing doses of pancuronium are much greater than those for fazadinium. However, it should be noted that the predicted recovery *gradients* for the two drugs are similar (see table IV for *observed* recovery rates). This appears to be the result of opposing influences: the pancuronium model has a steep concentration–effect slope and a slow concentration decay rate, whereas the fazadinium model exhibits a shallower concentration–effect slope and a more rapid concentration decay rate.

DISCUSSION

Pharmacokinetic data for fazadinium (tables I and V)

The decay curves fitted to the concentration–time data should be compared with those published by Tyers (1978) and Duvaldestin and colleagues (1978). In this study, all curves showed a rapid initial decline ($T_{\frac{1}{2}}^{\alpha} = 2.12 \pm 0.44$ min) followed by a slower terminal decay ($T_{\frac{1}{2}}^{\beta} = 41.99 \pm 5.85$ min). The value for $T_{\frac{1}{2}}^{\alpha}$ is greater than that observed by Tyers (0.83 min), but much lower than that reported by Duvaldestin (12.3 ± 2.5 min). Our value for $T_{\frac{1}{2}}^{\beta}$ is also significantly smaller than that reported by Duvaldestin (41.99 ± 5.85 compared with 76.4 ± 6.4 min).

Much of the difference between these results is a result of the great natural variation between subjects, but it should be noted that the sampling frequencies were not comparable, since Duvaldestin's group took only three samples in the first 20 min, whereas we took seven. It is evident that a rapid initial decay will not be detected if samples are not taken during the period of greatest change. (Similar differences are to be found in reports on other drugs; for instance $T_{\frac{1}{2}}^{\alpha}$ for tubocurarine has been reported as 0.93 min (Wingard and Cook, 1976), 6.93 min (Gibaldi, Levy and Hayton, 1972) and 18.3 min (Shanks, Ramzan and Triggs, 1979).) In the present study, sampling ceased at 120 min, whereas Duvaldestin's group continued until 300 min. It is likely that these later values contributed to a longer estimate of terminal half-time, and that the data from 1 to 300 min could be better fitted to a three-compartment model, as has been reported for tubocurarine (Gibaldi, Levy and Hayton, 1972).

However, we would emphasize that curve fitting is notoriously inexact, especially when performed by a simple "stripping" method (Riggs, 1963), so that a variety of feasible solutions may often be found to a single set of concentration–time data. Here, by a formal analysis of probability, the "most likely" function was derived for each set of data. Even so, it is difficult to state that a particular curve is more "correct" than another with similar fitting probability, so that different computational methods may arrive at widely differing solutions. Only when the chosen function fits the data perfectly will all methods agree.

Pharmacokinetic data for pancuronium (tables II and V)

Following a bolus dose, the initial decay is rapid ($T_{\frac{1}{2}}^{\alpha} = 5.18$ min), in agreement with the value of less than 5 min reported by Agoston and others (1973). This phase is followed by a more gradual terminal slope ($T_{\frac{1}{2}}^{\beta} = 100.17 \pm 7.41$ min); in agreement with values of 132 ± 24.9 (Somogyi, Shanks and Triggs, 1977), 114.3 ± 9.6 (Duvaldestin et al., 1978), 110 ± 20 (Miller at al., 1978) and 100.4 ± 3.2 min (McLeod, Watson and Rawlins, 1976).

Clearance was estimated to be 4.11 ± 0.60 litre h^{-1}, (1.024 ± 0.15 ml kg^{-1} min^{-1}) which compares to 4.44 ± 0.48 litre h^{-1} (McLeod, Watson and Rawlins, 1976), 4.27 ± 0.54 litre h^{-1} (McLeod, Hull and Watson, 1979) and 1.76 ml kg^{-1} min^{-1} (Miller et al., 1978).

As in all other reports, the apparent volumes of distribution (V^{ss}) showed considerable variation. The mean value of 131 ± 7.9 ml kg^{-1} (derived from table II)* compares closely to 132 ± 19 ml kg^{-1} obtained by McLeod, Watson and Rawlins (1976), but is significantly smaller than the value of 216 ± 10.6 ml kg^{-1} obtained by the same group on another series of subjects (McLeod, Hull and Watson, 1979).

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* Whilst difficult to justify, V^{ss} is expressed here in terms of ml kg^{-1} in order to facilitate comparison with other published data.

Pharmacodynamics

Since log-concentrations in all compartments of a mammillary open model decline at the same rate (β) during the terminal offset phase (see fig. 1), plasma concentration–effect studies can be used to determine the gradient of a Hill-plot, but a value for EC_{50} thus obtained will always underestimate that in the biophase. Only when the model is at steady state (after a long constant-rate infusion) can plasma be considered to be in equilibrium with the biophase.

In an infusion study on pancuronium (but not at steady state), Shanks, Somogyi and Triggs (1979) estimated the Hill-plot gradient (s) to range between 4.18 and 17.00, and EC_{50} to be 0.25 $\mu g\ ml^{-1}$. By contrast, Agoston, Feldman and Miller (1979) (in a similar study) found EC_{50} to be 0.14 $\mu g\ ml^{-1}$, and by calculation from their data, $s = 3.63$.

It is of particular interest that while both s and EC_{50} for pancuronium are by all accounts highly variable, those for fazadinium appear to be relatively consistent, so that variation in response is likely to result from pharmacokinetic, rather than pharmacodynamic factors. It is possible that the apparent variation in the concentration–effect relationship for pancuronium may be attributable to a variable degree of metabolism to 3–OH–pancuronium, which is less active but is not distinguished from the parent drug during the assay procedure (Agoston et al., 1977).

It is tempting to speculate that the Hill-plot gradient (s) may indicate the order of reaction (the number of antagonist molecules required to block one ion channel). However, the relationship between biophase concentration and response is almost certainly multifactorial, so that it is safer to regard the gradient as an empirically derived transfer function.

The relationship between dose and effect

The relationship between concentration and effect can be readily appreciated by reference to quadrant B of figure 5, which is simply a graphical representation of equation (5).

When concentrations are low, and do not reach point "R", receptors are occupied according to the conventional expression:

$$Y = \frac{[D]}{[D] + K_D}$$

(where Y is the fraction of receptors occupied, $[D]$ is the molar drug concentration, and K_D the equilibrium dissociation constant), but no appreciable effect (<2%) occurs. Therefore, point "R" corresponds to the "margin of safety" for adductor pollicis (where all the "spare" receptors are occupied by antagonist) (Paton and Waud, 1967).

Above point "S", which corresponds to the concentration required to produce a 98% effect, further increases in concentration can produce, at most, a further 2%. This range of concentrations can be considered to constitute a "pharmacokinetic zone", where receptor saturation is effectively complete. When the biophase concentration is above point "S", the duration of complete block will depend exclusively upon pharmacokinetic factors. However, once recovery begins (concentration is less than "S"), the *rate* of recovery depends upon both the biophase concentration decay rate and the sigmoidicity of the concentration–effect curve, so that the range of concentrations between "R" and "S" can be considered to constitute a "pharmacodynamic zone".

Thus, after a large dose ($ED_{90} \times 3$), the pancuronium concentration curve (fig. 5Ⓑ reaches point "S" after 75 min, and decays through the pharmacodynamic zone with a half-life of 94.5 min ($T_{\frac{1}{2}}{}^{\beta}$). By contrast, the fazadinium concentration curve reaches "S" after 30 min, and then decays with a half-life of only 48.8 min. However, inspection of the "$ED_{90} \times 3$" effect curves shows that the predicted *rates* of twitch recovery are almost identical. (Table IV shows that the measured twitch recovery rates for fazadinium and pancuronium do not differ significantly.) If smaller doses (ED_{90}) are given, the biophase concentration curve falls through the pharmacodynamic zone more rapidly (since it is heavily influenced by the distributive (α) phase), resulting in a steeper twitch recovery gradient.

It is now possible to explain the differences in potency ratio (between EC_{50} and ED_{90}) in similar terms. Referring to the examples in figure 5, values of EC_{50} for fazadinium and pancuronium are 0.909 and 0.23 $\mu g\ ml^{-1}$ respectively, yielding a potency ratio of 3.95. The corresponding values of ED_{90} are 16.20 mg and 2.322 mg; here the ratio of 6.98 conforms with clinical observation (Lund and Stovner, 1970; Schuh, 1975). The difference between the ratios for EC_{50} and ED_{90} has both pharmacodynamic and pharmacokinetic origins. First, it can be calculated (equation (5)) that the *concentrations* for 90% effect (EC_{90}) are 1.374 and 0.292 $\mu g\ ml^{-1}$ (fazadinium and pancuronium respectively), yielding a potency ratio of 4.71. The increase in potency ratio from 3.95 (EC_{50}) to 4.71 (EC_{90}) is simply a result of the difference between the slopes of the concentration–effect characteristics for the two drugs.

However, there remains a difference between the potency ratio for *concentration* (4.71) and that for the *dose* (6.98) required to produce a 90% effect. Since, as already stated, V_2, k_{12} and k_{10} for fazadinium are all greater than for pancuronium, a greater proportion of the dose leaves the central compartment during the redistributive phase, so that the concentration gradient between plasma and biophase declines more rapidly. Thus the peak biophase concentration (where plasma and biophase concentration curves intersect) is a lower proportion of initial concentration for fazadinium than for pancuronium. Therefore, relatively more fazadinium than pancuronium must be given to achieve equally effective biophase concentrations.

It can be postulated that these characteristics are also responsible for the more rapid onset of fazadinium. Despite a slower biophase half-life ($T_{\frac{1}{2}}^{\gamma}$ in table V), the biophase concentration for fazadinium increases more rapidly than for pancuronium as a result of the (proportionately) much greater plasma concentration during the first few minutes after administration of a bolus dose (taking the examples in figure 5, a dose of $ED_{90} \times 2$ will yield a 90% block in the fazadinium model within 1.35 min, compared with 1.70 min in the pancuronium model). It should be noted that, whereas the onset time is dose-dependent, the time at which both effect and biophase concentration reach their peak is dose-independent. Thus it can be seen that, in the fazadinium and pancuronium models of figure 5, maximum effect (and biophase concentration) occur after 6.5 and 8.2 min respectively, regardless of dose.

Further development of pharmacodynamic models

The simple biophase model is based upon the assumptions (Furchgott, 1955) that drug enters and leaves a homogenous activity compartment by a single, isotropic, first order process, and that a negligible proportion of drug in the biophase is bound to either receptor or non-specific sites. The hypothesis is supported by the findings that the Hill-plots are linear with minimal hysteresis.

Although the model is compatible with Waud's (1968) concept of an access-limited biophase, no assumptions are made as to the *nature* of the rate-limiting process; only that it can be characterized by first-order differential equations.

Since it has been demonstrated conclusively (Armstrong and Lester, 1979) that, despite high affinity, tubocurarine dissociates from receptor complexes very rapidly (within milliseconds), there is no remaining basis for the theory (Feldman and Tyrrell, 1970) that slow, non-competitive dissociation rather than access-limitation provides the rate-limiting step for the offset of activity. Therefore, for the purpose of this model it is safe to assume that drug in the biophase is in constant equilibrium with receptors. With less certainty, it is also assumed that receptor uptake has a negligible effect upon the "virtual space" of the biophase. It is possible to develop the model to account for a biophase volume which varies with receptor uptake (Rang, 1966; Thron and Waud, 1968). Unfortunately, this would render the model non-linear, thus precluding (at present) explicit solution. Such a model could be solved by numerical or analog computation, but both techniques are cumbersome and inexact, and would be introduced only if the observed data could not be satisfied by any other means.

At present, the effects of plasma protein binding are assumed to be constant, and are ignored. Oyston (1979) has shown that the proportion (approximately 30%) of pancuronium bound to plasma proteins does not vary over the clinical range of concentrations.

Therefore it must be emphasized that the computed "biophase" concentrations in the present models are "apparent" rather than "real". In fact, they represent the concentration of drug that would be found in plasma if it were in equilibrium with the biophase, so that the effects of binding or solubility partition can be ignored. Thus it is not possible to estimate the "real" biophase concentration without correcting for protein binding. Fortunately, the negligible quantity of drug in the biophase allows this correction to be made by simple proportion, so that if pancuronium is 30% bound, the "free" concentration is 70% of the "apparent" concentration.

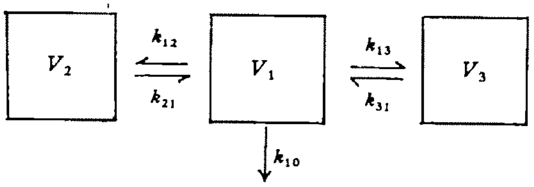
If it is assumed that fazadinium is 35% bound to plasma proteins (Oyston, 1979), and receptor occupancy is 0.866 at 50% effect (Y_{50} (Waud, 1977)), the dissociation constant (K_D) can be estimated, since it equates with the molar concentration at 50% occupancy. Taking the mean value of EC_{50} from table IV ($1.005\ \mu g\ ml^{-1}$), and correcting for plasma protein binding, $K_D = 0.14 \times 10^{-6}$ mol litre^{-1}.

This is less than Waud's estimate of 0.377×10^{-6} mol litre^{-1} from organ-bath studies on guineapig lumbrical muscle, but if consideration is given to the variation in K_D between species, and in Y_{50} between different muscles of the same species demonstrated for tubocurarine (Bowen, 1972; Waud and Waud, 1972), the values are not incompatible.

After single bolus doses, the onset and decay characteristics of both fazadinium and pancuronium can be characterized by linear, first-order biophase models. Comparison of these models suggests that despite widely differing pharmacokinetic profiles, both drugs may exhibit similar durations of effect at certain doses, as a result of the combined effects of kinetic and dynamic factors. Over a wider range of doses, it is clear that pancuronium is more cumulative, with a longer duration of action than fazadinium. Since it has been shown that the potency ratio for fazadinium and pancuronium varies widely depending upon the specified conditions, great care must be taken in establishing comparable doses if misleading clinical impressions are to be avoided. This can only be achieved by the use of a full-range pharmacodynamic model, by which indices such as EC_{50}, ED_{50} and ED_{90} can be estimated.

APPENDIX

A general solution for bolus doses into a three-compartment open (mammillary) model:



Given values for volumes and rate constants (above), the three-compartment solution previously described (Hull et al., 1978) allowed the calculation of the drug concentrations in each compartment for any time t, following a bolus dose into V_1; given that the model was previously "empty". More complex initial conditions could not be specified, so that it was not possible to calculate the effects of increments, or of dividing the dose between two or more compartments.

The procedure described here overcomes these restrictions, as equations are presented for all compartmental concentrations following any specified set of initial conditions.

The concentrations in each compartment at time t are characterized by the equations:

$$C_1 = A.e^{-\alpha t}+B.e^{-\beta t}+D.e^{-\gamma t} \tag{1}$$

$$C_2 = P\ e^{-\alpha t}+Q\ e^{-\beta t}+R.e^{-\gamma t} \tag{2}$$

$$C_3 = L\ e^{-\alpha t}+M\ e^{-\beta t}+N\ e^{-\gamma t} \tag{3}$$

The coefficients α, β and γ must first be found. By Laplacian transformation of the basic differential equations, matrix solution, and reverse transformation, the following cubic equation can be derived:

$$s^3+s^2p+sq+r = 0 \tag{4}$$

where

$$p = k_{31}+k_{21}+k_{12}+k_{13}+k_{10} \tag{5}$$

$$q = k_{21}k_{31}+k_{12}k_{31}+k_{13}k_{21}+k_{10}k_{31}+k_{10}k_{21} \tag{6}$$

$$r = k_{21}k_{31}k_{10} \tag{7}$$

s = the Laplacian operator

$-\alpha$, $-\beta$ and $-\gamma$ are the roots of equation (4), and for any physically realizable model will be real.

The roots can be found by the method described by Hodgman (1957), which first reduces equation (4) to

$$x^3+ax+b = 0 \tag{8}$$

by substituting for s the value $\left(x-\frac{p}{3}\right)$

Here $a = \frac{1}{3}(3q-p^2)$ and $b = \frac{1}{27}(2p^3-9pq+27r)$.

The three roots of (8) can now be found:

$$x_1 = 2\sqrt{-\frac{a}{3}}.\cos\frac{\theta}{3} \tag{9}$$

$$x_2 = 2\sqrt{-\frac{a}{3}}\ \cos\left[\frac{\theta}{3}+120°\right] \tag{10}$$

$$x_3 = 2\sqrt{-\frac{a}{3}}\ \cos\left[\frac{\theta}{3}+240°\right] \tag{11}$$

where

$$\cos\theta = -\frac{b}{2}\bigg/\sqrt{-\frac{a^3}{27}} \tag{12}$$

Then

$$s_1 = x_1-\left[\frac{p}{3}\right],\quad s_2 = x_2-\left[\frac{p}{3}\right]\quad \text{and}\quad s_3 = x_3-\left[\frac{p}{3}\right]$$

Finally

$$\alpha = -s_1,\quad \beta = -s_2\quad \text{and}\quad \gamma = -s_3$$

Given values for α, β and γ, which remain unchanged for any specified model, the constants $A \rightarrow N$ can be found for any set of initial conditions.

Let the initial concentrations in compartment 1, 2 and 3 be ψ_1, ψ_2 and ψ_3 respectively. Then for a single bolus dose into

V_1 of an empty model,

$$\psi_1 = \frac{Xd}{V_1}, \psi_2 = 0, \quad \text{and} \quad \psi_3 = 0$$

Then for compartment 1:

$$A = \frac{\psi_1 . \alpha^2 - \alpha Y + Z}{(\alpha-\gamma)(\alpha-\beta)} \tag{13}$$

$$B = \frac{\psi_1 . \beta^2 - \beta Y + Z}{(\gamma-\beta)(\alpha-\beta)} \tag{14}$$

$$C = \frac{\psi_1 . \gamma^2 - \gamma Y + Z}{(\gamma-\beta)(\gamma-\alpha)} \tag{15}$$

where

$$Y = \psi_1(k_{21}+k_{31}) + \psi_2 k_{12} + \psi_3 k_{13}$$

and

$$Z = \psi_1 k_{21} k_{31} + \psi_2 k_{12} k_{31} + \psi_3 k_{13} k_{21}$$

For compartment 2,

$$P = \frac{\psi_2 . \alpha^2 - \alpha Y' + Z'}{(\alpha-\gamma)(\alpha-\beta)} \tag{16}$$

$$Q = \frac{\psi_2 . \beta^2 - \beta Y' + Z'}{(\gamma-\beta)(\alpha-\beta)} \tag{17}$$

$$R = \frac{\psi_2 . \gamma^2 - \gamma Y' + Z'}{(\gamma-\beta)(\gamma-\alpha)} \tag{18}$$

where

$$Y' = \psi_2(k_{31}+k_{12}+k_{13}+k_{10}) + \psi_1 k_{21}$$

and

$$Z' = \psi_2 k_{31}(k_{12}+k_{10}) + \psi_1 k_{21} k_{31} + \psi_3 k_{13} k_{21}$$

For compartment 3,

$$L = \frac{\psi_3 \alpha^2 - \alpha Y'' + Z''}{(\alpha-\gamma)(\alpha-\beta)} \tag{19}$$

$$M = \frac{\psi_3 \beta^2 - \beta Y'' + Z''}{(\gamma-\beta)(\alpha-\beta)} \tag{20}$$

$$N = \frac{\psi_3 \gamma^2 - \gamma Y'' + Z''}{(\gamma-\beta)(\gamma-\alpha)} \tag{21}$$

where

$$Y'' = \psi_3(k_{21}+k_{13}+k_{12}+k_{10}) + \psi_1 k_{31}$$

and

$$Z'' = \psi_3 k_{21}(k_{13}+k_{10}) + \psi_1 k_{31} k_{21} + \psi_2 k_{12} k_{31}$$

Equations (1)–(3) can now be solved for any time t.

Incrementation

To calculate the effect of an increment given at time t^n following the initial dose at time t^0, the concentrations $C_1{}^n$, $C_2{}^n$ and $C_3{}^n$ are determined using equations (1)–(3). Assuming that the increment is to be added to the central compartment, new values of ψ are calculated:

$$\psi_1 = C_1{}^n + \frac{X_{\text{incr}}}{V_1}$$

$$\psi_2 = C_2{}^n$$

$$\psi_3 = C_3{}^n$$

Constants $A \rightarrow N$ are calculated (equations (13)–(21)), thus permitting solution of equations (1)–(3). It must be remembered that the "t" in these equations refers to the elapsed time since t^n, so that t^n should be subtracted from the total elapsed time. This process can be repeated indefinitely, for any incremental dose at any time, so that the method is more flexible than the "multiple dosing" procedures described previously (Gibaldi and Perrier, 1975). It is important that calculations of this type are performed to high precision if cumulative rounding errors are to be avoided.

The biophase model

When compartment 3 is assumed to be a "negligible biophase", equations (13)–(21) can be simplified by removal of any term which is the product of k_{13}, since in this case $k_{13} = 0$.

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FAZADINIUM ET PANCURONIUM: UNE ÉTUDE PHARMACODYNAMIQUE

RESUME

Les propriétés du fazadinium et du pancuronium de provoquer le blocage neuromusculaire ont fait l'objet d'une comparaison basée sur un modèle pharmacodynamique général. Etant donné que celui-ci permet de caractériser le rapport global entre la dose et les effets, il est possible de l'utiliser pour déterminer avec précision les doses de puissance égale, comparer les courbes temps–effets et faire concorder les propriétés cliniques et pharmacocinétiques apparemment contradictoires de ces deux substances. Le fazadinium s'est avéré avoir une durée plus courte que le pancuronium et semblait être sujet à des variations moindres entre les sujets. Le rapport de puissance variait entre 3,4 : 1 et 7,2 : 1 selon la définition choisie. On présente en annexe une solution générale pour le modèle mamillaire ouvert à trois compartiments dans n'importe quel ensemble de conditions initiales. Ces équations permettent de calculer explicitement tout type d'accroissement de substance dans l'un quelconque des compartiments du modèle.

FAZADINIUM UND PANCURONIUM—EINE PHARMAKODYNAMISCHE STUDIE

ZUSAMMENFASSUNG

Die neuromuskulären Blockierungseigenschaften von Fazadinium und Pancuronium wurden mittels eines allgemeinen pharmakodynamischen Modells verglichen. Da das Modell das Gesamtverhältnis zwischen Dosis und Effekt charakterisiert, kann es dazu verwendet werden, genau gleich starke Dosen zu bestimmen, Zeit Effekt-Kurven zu vergleichen und die anscheinend widersprechenden klinischen und pharmakokinetischen Eigenschaften der beiden Mittel zu vereinbaren. Es zeigte sich, dass Fazadinium eine kurzere Wirkungsdauer als Pancuronium hat; Fazadinium schien auch weniger Variationen zwischen den einzelnen Versuchspersonen aufzuweisen. Das Starkeverhaltnis wechselte zwischen 3,4 : 1 und 7,2 : 1, je nach der gewahlten Definition. Eine allgemeine Losung fur das offene mamillare Dreifächermodell, aufbauend auf einen beliebigen Satz von Ausgangsbedingungen, wird in der Form eines Anhangs dargeboten. Diese Gleichungen erlauben eine klare Berechnung und Addition eines beliebigen Dosissteigerungsbildes in ein beliebiges Fach des Modells.

FAZADINIO Y PANCURONIO: UN ESTUDIO FARMACODINÁMICO

SUMARIO

Se llevó a cabo una comparación de las características bloqueadoras neuromusculares del fazadinio y del pancuronio al usar un modelo farmacodinámico general. Puesto que caracteriza a la relación global entre la dosis y el efecto, el modelo puede utilizarse para determinar con precisión dosis equipotenciales, comparar las curvas tiempo–efecto y ajustar las características clínicas y farmacoquinéticas de las dos substancias aparentemente contradictorias. El fazadinio demostró tener una duración menor que la del pancuronio y pareció presentar menos variaciones entre los sujetos. La relación de potencia variaba entre 3,4 : 1 y 7,2 1, dependiendo de la definición escogida. Se somete en el apéndice una solución general para el modelo mamilar abierto de tres divisiones después de cualquier juego de condiciones iniciales. Estas ecuaciones permiten el cómputo explícito de cualquier forma de gradación de la substancia dentro de cualquier división del modelo.

Br. J. Anaesth. (1980), 52, 1223

TEMPERATURE MONITORING DURING GENERAL ANAESTHESIA

B. D. CROCKER, F. OKUMURA, D. I. McCUAIG AND M. A. DENBOROUGH

SUMMARY

A study of core temperature monitoring during general anaesthesia indicates that this can be introduced as a routine procedure in order to reduce mortality from malignant hyperpyrexia. The temperature profiles of 2410 patients are presented. Both mean rectal and mean oesophageal temperatures decreased during general anaesthesia. The mean oesophageal temperatures were on average 0.6 °C less than the mean rectal temperatures during the first hour of anaesthesia. An increase in core temperature occurred in nearly 20% of patients. This appeared to be related to an initially low body temperature. Core temperatures during general anaesthesia were significantly greater in patients who received the combination of suxamethonium and halothane than in patients receiving other drugs. This observation is of theoretical interest and suggests that the increase of temperature in malignant hyperpyrexia may be an exaggeration of a normal response to these agents.

Despite increasing awareness of malignant hyperpyrexia (MH) the mortality from this complication remains about 70%. Mortality in MH is directly related to the duration of exposure of the susceptible individual to the harmful anaesthetic (King and Denborough, 1973) and early diagnosis of MH is important so that the offending anaesthetic can be stopped and treatment started. In the absence of a simple routine predictive test, the simplest and most effective means of making an early diagnosis of MH might be routine temperature monitoring during general anaesthesia.

The anaesthetists at the Royal Canberra Hospital took part in a study over 12 months which was designed to assess the use of routine temperature monitoring during general anaesthesia.

METHODS

The study was carried out in the operating theatres of the Royal Canberra Hospital. Standardization of conditions was not attempted as it was intended that the results should represent information obtained from routine theatre procedures, and should reflect a realistic estimate of what can be expected in routine practice.

The skin preparations used during the operations were either spiritous or aqueous chlorhexidine, or 0.1% chlorhexidine with 1% cetavlon. Draping of the patient was consistent with standard surgical procedures.

The temperature and humidity of the theatres were maintained at 22 °C and 60% respectively. The mean theatre temperature, recorded by wall-mounted mercury thermometers, was 21.8 °C (SD ± 1.1 °C) with a range of 19–25 °C.

The inhalation anaesthetics were delivered either by CIG (Commonwealth Industrial Gases) or Dräger anaesthetic equipment.

Measurement of body temperature was made with a Medishield digital thermometer coupled to a flexible Yellow Springs Series 400 thermistor probe, which was inserted into either the rectum or the oesophagus by the anaesthetist or theatre staff. The choice of temperature site was made in the theatre before surgery. Only one site was used in each patient. A stable temperature was obtained about 4 min after the insertion of the thermocouple probe. For this reason, the first temperatures reported are at 10 min from when the measurements began. Temperature recordings, made from the onset of anaesthesia, were measured at 10-min intervals for the first 30 min and at 30-min intervals thereafter.

The types of operation were classified by the anaesthetists in eight groups (table I). Also recorded were age, sex, weight, position in which the operation was performed, premedication tempera-

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0007-0912/80/121223-07 $01.00

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TABLE I. *Types of operation*

Operation	Number of patients	% of total ($n = 2139$)
Thoracic	99	4.6
Head	104	4.9
Neck	50	2.3
Abdominal	807	37.7
Pelvic	89	4.2
Limbs	364	17.0
Surface	205	9.6
Minor	421	19.7

ture, site of temperature monitoring, premedication drugs, non-inhalation drugs, inhalation drugs, neuromuscular blockers, extra drugs used, i.v. and irrigation fluids administered, endotracheal intubation, warming or cooling measures, and humidification. All data were recorded, stored and processed on a Univac 1100/42 computer, using the statistical package, P-STAT, from Princeton University. *P*-values were obtained using a Student's *t* test programme run on a PDP8/I computer.

Measurements from a total of 2800 patients were obtained, but records from only 2410 patients contained data suitable for analysis. Within this group of 2410 patients, data for some of the variables which were being examined were missing. Temperature profiles are presented for both rectal and oesophageal sites.

RESULTS

The sex of the patient was recorded in all but three of the 2410 cases: 1024 (43%) were male and 1383 (57%) were female. Rectal temperatures did not differ significantly according to sex; in women, oesophageal temperatures were significantly greater than in men at 10 min ($P < 0.05$), 20 min ($P < 0.005$) and 30 min ($P < 0.05$).

The mean age in 2372 patients was 34.7 yr (SD ±20.97 yr, range 1–92). No significant difference in temperature profile was found when the data were divided according to decades. The mean weight in 2186 patients was 58.29 kg (SD ±21.51 kg, range 2–125 kg).

Temperature changes

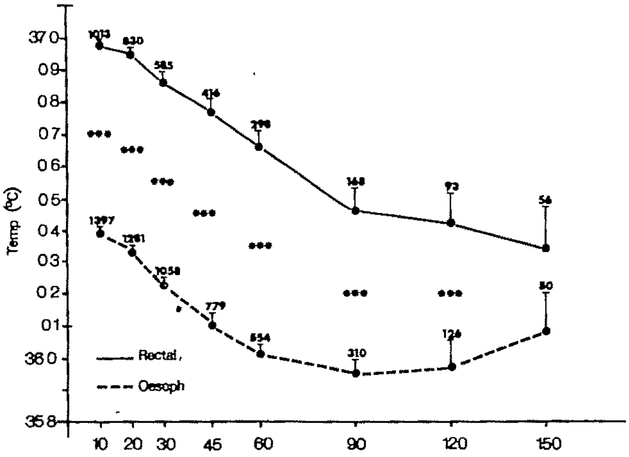

FIG. 1. Mean changes in rectal and oesophageal temperature with increasing duration of anaesthesia; number of patients. Vertical bars represent SEM. $^{***}P < 0.001$.

Decreases. Both rectal and oesophageal temperature decreased during general anaesthesia (fig. 1). Oesophageal temperatures were significantly lower than rectal temperatures for the first 2 h of anaesthesia (fig. 1). During the 1st hour, oesophageal temperatures were approximately 0.6 °C lower than rectal temperatures. Rectal temperature decreased at the same rate as oesophageal temperature for the 1st hour of anaesthesia (fig. 2). The mean decrease in rectal temperature was 0.3 °C ± 0.4 (SD) and the mean decrease in oesophageal temperature was 0.3 °C ± 0.5 (SD). From 60 to 90 min the rate of decrease in oesophageal temperature was significantly less than the rate of decrease in rectal temperature ($P < 0.01$).

Increases. The mean temperature increases at different intervals and the percentages of patients

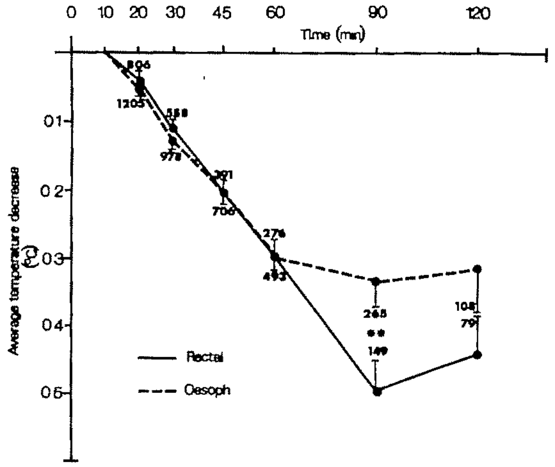

FIG. 2. Comparison of mean rates of decrease in rectal and oesophageal temperature with increasing duration of anaesthesia; the number of patients. Vertical bars represent SEM. $^{**}P < 0.01$.

TABLE II. *Increase in temperature in patients during anaesthesia*

Site	Time interval (min)	Number of patients	Percentage of patients	Temperature at 10 min (°C) Mean	SD	Range	Temperature at end of interval (°C) Mean	SD	Range	Increase (°C) Mean	SD	Range
Rectal	10–20	142	17	36.8	0.8	34.0–38.9	37.1	0.8	34.1–39.4	0.3	0.3	0.1–2.8
	10–30	110	19	36.8	0.9	34.0–38.9	37.1	0.8	34.1–39.2	0.3	0.4	0.1–2.9
	10–45	64	15	36.7	0.8	34.0–38.0	37.0	0.7	35.0–38.6	0.3	0.3	0.1–1.9
	10–60	37	12	36.6	0.9	34.0–38.0	37.0	0.8	35.0–38.6	0.4	0.4	0.1–2.0
	10–90	17	10	36.7	1.1	34.8–38.9	37.1	1.0	35.2–39.0	0.4	0.4	0.1–2.0
	10–120	11	11.8	36.5	1.0	34.8–38.0	37.0	0.8	35.8–38.5	0.5	0.4	0.2–1.8
Oesophageal	10–20	235	18	36.2	0.7	32.0–39.2	36.5	0.7	32.6–39.4	0.3	0.2	0.1–2.0
	10–30	192	18	36.2	0.9	32.0–38.5	36.5	0.7	33.0–38.8	0.3	0.3	0.1–2.0
	10–45	128	16	36.1	0.9	32.0–39.2	36.5	0.8	33.0–39.5	0.4	0.4	0.1–1.8
	10–60	89	16	36.2	0.6	34.3–37.8	36.6	0.6	35.1–38.2	0.4	0.4	0.1–1.9
	10–90	62	20	36.2	0.7	34.3–37.7	36.6	0.8	35.0–38.8	0.4	0.4	0.1–2.2
	10–120	32	25	36.2	0.7	34.4–37.7	36.6	0.8	35.1–38.3	0.4	0.3	0.1–1.7

experiencing temperature increases during these intervals are shown in table II. For anaesthetics lasting less than 90 min, between 10% and 20% of patients had an increase in temperature. The patterns were similar for both rectal and oesophageal measurements. The greatest rectal temperature reached was 39.4 °C and the greatest oesophageal temperature was 39.5 °C. The largest increase in rectal temperature was 2.9 °C and the greatest increase in oesophageal temperature was 2.2 °C. At both sites, for each of the time intervals up to 60 min, the mean initial temperatures (at 10 min) in those patients whose temperatures increased during anaesthesia were all significantly lower ($P < 0.01$) than the mean initial temperature in those patients who had no temperature increases.

Drugs

Premedicants. The belladonna drugs, hyoscine and atropine, used in conjunction with papaveretum, pethidine or morphine were the premedication drugs most frequently used in this study. Patients receiving premedication containing atropine had temperature profiles under anaesthesia similar to those receiving hyoscine. There were no significant differences in temperatures between patients receiving either of the belladonna drugs as premedication and those who did not.

Non-inhalation anaesthetics. Thiopentone was the most frequently used non-inhalation anaesthetic. Ketamine, propanidid, Althesin, methohexitone and the neuroleptanalgesic drugs (fentanyl and droperidol), chloropromazine and diazepam were used less frequently.

The temperatures of patients receiving ketamine were significantly greater at both the rectal and oesophageal sites than those of patients receiving thiopentone (fig. 3).

No abnormal temperature profiles were noted in patients receiving other non-inhalation anaesthetic drugs.

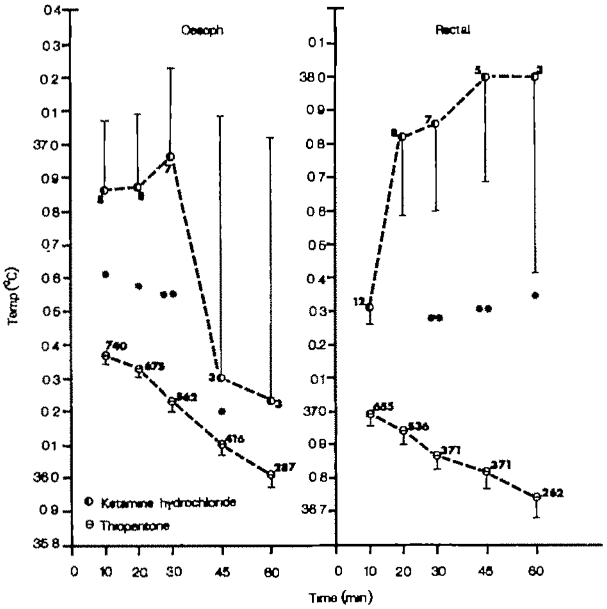

FIG. 3. Mean rectal and oesophageal temperature in patients who received ketamine ◐ and in those who received thiopentone ⊖; number of patients. Vertical bars represent SEM. $^{*}P < 0.05$; $^{**}P < 0.01$.

Neuromuscular blockers. The neuromuscular blockers used during this study were classified either as non-depolarizing or depolarizing. Suxamethonium was the neuromuscular blocker used most commonly and the only depolarizing agent. The non-depolarizing agents in order of decreasing use were alcuronium, pancuronium and tubocurarine, and gallamine.

For the first 30–45 min of anaesthesia, patients who received suxamethonium as the sole neuromuscular blocker had significantly higher oesophageal and rectal temperatures ($P<0.05$) than those receiving non-depolarizing neuromuscular blockers (fig. 4). Patients who received suxamethonium as the sole neuromuscular blocker had significantly higher oesophageal temperature ($P<0.05$) for the first 30 min of anaesthesia than those patients who received no neuromuscular blockers (fig. 5). Rectal temperatures showed a similar pattern. No difference in temperature at either site was observed between patients receiving non-depolarizing neuromuscular blockers and those receiving none at all.

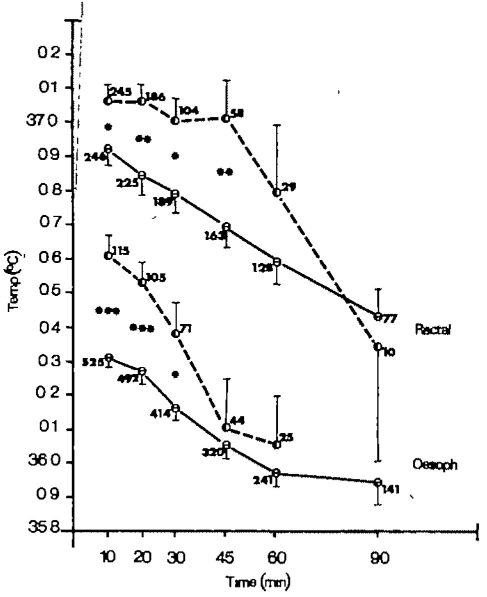

FIG. 4. Mean rectal and oesophageal temperature in patients who received suxamethonium ◐—◐ and in those who received non-depolarizing neuromuscular blockers ⊖——⊖; number of patients. Vertical bars represent SEM. $*P<0.05$; $**P<0.01$; $***P<0.001$.

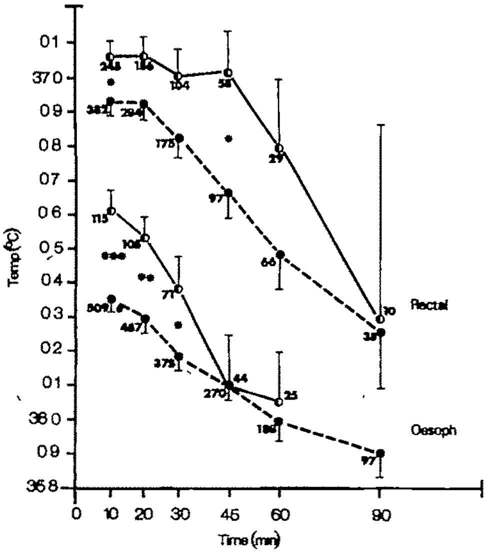

FIG. 5. Mean rectal and oesophageal temperature in patients who received suxamethonium ◐——◐ and in those who received no neuromuscular blockers ●—●; number of patients. Vertical bars represent SEM. $*P<0.05$; $**P<0.01$; $***P<0.001$.

The temperature differences between patients receiving suxamethonium and those receiving either non-depolarizing neuromuscular blockers or none at all were found to be dependent on the presence of halothane (figs 6, 7). When halothane was not administered no significant temperature differences occurred.

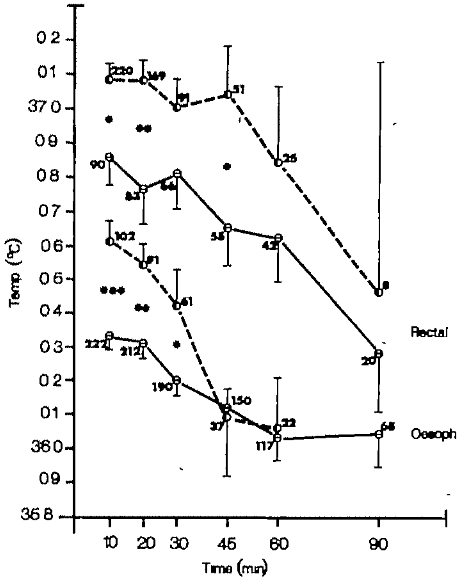

FIG. 6. Mean rectal and oesophageal temperature in patients who received suxamethonium and halothane ◐—◐ and in those who received non-depolarizing neuromuscular blockers and halothane ⊖——⊖; number of patients. Vertical bars represent SEM. $*P<0.05$; $**P<0.01$; $***P<0.001$.

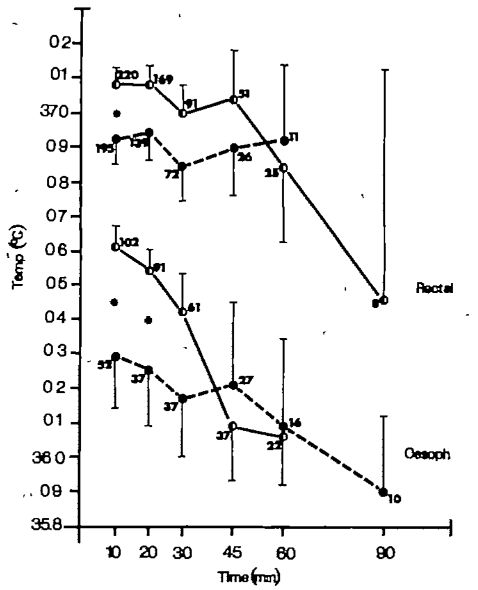

FIG. 7. Mean rectal and oesophageal temperature in patients who received suxamethonium and halothane ◐——◐ and in those who received halothane but no neuromuscular blockers ●—●; number of patients. Vertical bars represent SEM. $*P<0.05$.

Inhalation agents. The inhalation agents used in this study were nitrous oxide, halothane, ether and methoxyflurane. Only one patient was given methoxyflurane and two received ether.

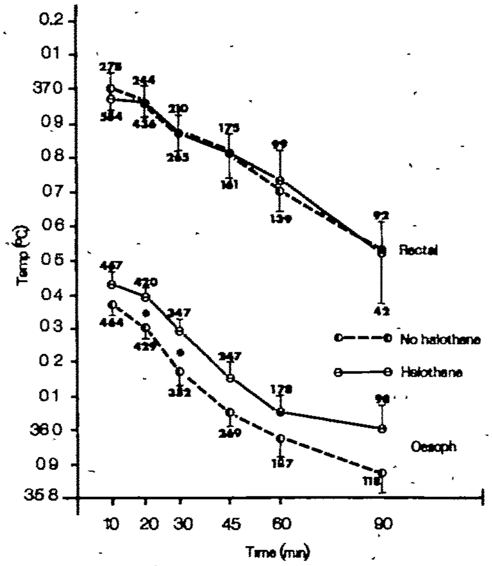

FIG. 8. Mean rectal and oesophageal temperature in patients who received halothane, nitrous oxide and oxygen and in those who received nitrous oxide and oxygen without halothane; number of patients. Vertical bars represent SEM. $*P<0.05$.

The mean oesophageal temperatures of patients who received halothane, nitrous oxide and oxygen were significantly greater at 20 and 30 min ($P<0.05$) than those patients who were given nitrous oxide and oxygen without halothane. No such differences were seen in the rectal temperatures (fig. 8).

DISCUSSION

The experience gained in this investigation indicates core temperature monitoring can be introduced as a routine procedure during anaesthesia.

The results confirm earlier observations that during general anaesthesia the core temperature usually decreases. Morris (1971) observed that anaesthetized patients remained normothermic in environmental temperatures of 24 °C and more. The ambient temperature of the operating theatres in the present study was 21.8 °C, so the overall reduction in temperature at both rectal and oesophageal sites was predictable.

During the 1st hour of anaesthesia rectal temperature was, on average, 0.6 °C higher than oesophageal temperature. This difference is similar to the results found in awake patients in earlier investigations (Tanner, 1951; Cranston, Gerbrandy and Snell, 1954). It seems that the factors governing temperature difference between the two sites are maintained during anaesthesia. Whilst it is possible that some of the oesophageal leads may have been misplaced in the present investigation and were really reflecting nasopharyngeal or sublingual temperatures, there is little difference in temperature measurements at these three different sites (Cranston, Gerbrandy and Snell, 1954; Morris and Wilkey, 1970). The changes at both sites in the rate of decrease of temperature after 60 min of anaesthesia are interesting and may reflect thermoregulatory responses to reduced body temperatures. Previous investigations have shown that changes in body temperature are reflected more quickly by oral and oesophageal than by rectal measurements (Gerbrandy, Snell and Cranston, 1954) which may explain the slower rate of change observed at the rectal site.

Some increase in core temperature was noted in 10–20% of patients in this study. The temperature increases occurred in patients who began with a lower than average core temperature, and probably reflect a thermoregulatory response to this lower initial body temperature. No other special characteristics were found in this group of patients.

The use of atropine and hyoscine was not associated with an increase in temperature during general anaesthesia. This agrees with earlier observations that the suppression of sweating caused by atropine is not significant when the ambient temperature is below body temperature (Magbagbeola, 1973), and that the administration of hyoscine 0.4 mg did not produce an increase in temperature although the rate of sweating was diminished by 35% (Frumin and Papper, 1951).

Ketamine produced a significant increase in core temperature during anaesthesia, a finding which has been observed previously (Engelman and Lockhart, 1972). Although ketamine has been used successfully in patients who are susceptible to MH (Wadhwa and Tantisira, 1974), its use, particularly in combination with suxamethonium and halothane, has been questioned (Mogensen, Misfeldt and Hanel, 1974; Roervik and Stovner, 1974). It has been suggested that ketamine should not be used when muscular relaxation is required since it causes muscular hypertonicity (Sussman, 1974).

Halothane is the anaesthetic agent most commonly implicated in MH, and it is interesting that in this study oesophageal temperature was significantly higher for the first 30 min in patients who received halothane compared with those who did not.

Another drug commonly implicated in MH is suxamethonium. The observation that patients who received suxamethonium had significantly higher core temperatures during general anaesthesia than those who received other neuromuscular blockers, or none at all, is interesting. This increase in temperature lasted for the first 30 min of general anaesthesia and may have resulted from the muscle fasciculations which follow i.v. injection of suxamethonium. Small increases in body temperature and hyper-rigidity have been observed previously in children following injections of suxamethonium (Innes and Strømme, 1973).

A more detailed examination of the increase in temperature induced by suxamethonium has shown that this occurred only in those patients who received halothane in addition to suxamethonium. This suggests that there may be a synergistic effect between suxamethonium and halothane to produce the increase in body temperature. The fact that this occurs in apparently normal individuals raises the possibility that MH may result from an exaggeration of this normal response.

ACKNOWLEDGEMENTS

We are indebted to all the anaesthetists at the Royal Canberra Hospital who collaborated in this investigation. They were: Drs P. N. Booth, P. J. Christie, K. E. Downes, G. M. Jerogin, M. J. Kneebone, H. M. Lawrence, S. Leitch, T. G. Lithgow, H. Lopert, J. G. Major, B. D. Morison, J. M. Purchas, P. Quach, C. G. Russell-Jones, P. I. Rylands, D. P. Wallner, and A. D. Witheford. We are also indebted to Sister M. Dockar and the Nursing Staff for all their help. We are also very greatful to Medishield (N.S.W.) for generously providing the electronic thermometers used in the investigation and to ICI Australia Limited, to Glaxo Australia Pty Ltd, and to Medishield (N.S.W.) for generous financial assistance.

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SURVEILLANCE ET CONTROLE DE LA TEMPERATURE AU COURS DE L'ANESTHESIE GENERALE

RESUME

Une étude de la surveillance de température intérieure au cours de l'anesthésie générale démontre que l'on peut inclure cette opération en tant que contrôle de routine afin de réduire la mortalité due à l'hyperpyrexie maligne. Les profils de température de 2410 patients sont soumis. Au cours de l'anesthésie générale, tant la température rectale que la température oesophagique ont diminué. Les températures oesophagiques moyennes se situaient en moyenne à 0,6 °C au-dessous des températures rectales moyennes au cours de la première heure de l'anesthésie. Chez presque 20% des patients, la température intérieure subit une augmentation. Ceci semble être fonction d'une température corporelle initiale basse. Les températures intérieures au cours de l'anesthésie générale étaient de beaucoup supérieures chez les patients qui avaient reçu un mélange de suxaméthonium et d'halothane que chez les patients auxquels on avait administré d'autres substances. Cette remarque présente un intérêt théorique et amène à penser que l'augmentation de température au cours de l'hyperpyrexie maligne peut représenter une exagération de la réponse normale à ces agents.

TEMPERATURÜBERWACHUNG WÄHREND DER ALLGEMEINNARKOSE

ZUSAMMENFASSUNG

Studien über die Temperaturüberwachung während der allgemeinnarkose deuten an, dass diese Massnahme gewohnheitsmässig eingeführt werden könnte,, um die Sterblichkeit infolge bösartiger Hyperpyrexie zu reduzieren. Die Temperaturverlaufsbilder von 2410 Patienten werden vorgestellt. Wahrend der Allgemeinnarkose gingen die mittleren Rektum- und Speiseröhrentemperaturen zuruck. Wahrend der ersten Stunde der Anästhesie waren die mittleren Speiserohrentemperaturen im Durschnitt 0,6 °C niedriger als die mittleren Rektumtemperaturen. Eine Erhöhung der Temperatur stellte sich bei fast 20% der Patienten ein. Diese Erhöhung schien mit einer ursprünglich niedrigen Körpertemperatur zusammenzuhängen. Temperaturen während der Allgemeinnarkose waren bedeutend grösser bei Patienten, die eine Kombination von Suxamethonium und Halothan bekommen hatten als bei Patienten, die andere Mittel bekamen. Die Beobachtung ist von theoretischem Interesse und deutet an, dass die Erhöhung der Temperatur bei bösartiger Hyperpyrexie eventuell eine Übertreibung einer normalen Reaktion auf diese Mittel sein könnte.

CONTROL DE LA TEMPERATURA DURANTE LA ANESTESIA GENERAL

SUMARIO

Un estudio del control de la temperatura interna en el curso de la anestesia general indica que éste podría incluirse como procedimiento rutinario con miras a reducir la mortandad debida a la hiperpirexia maligna. Se presentan perfiles de temperatura de 2410 pacientes. Ambas temperaturas rectal media y esofágica media bajaron durante la anestesia general. En promedio, las temperatures esofágicas medias se hallaban a 0,6 °C por debajo de las temperaturas rectales medias durante la primera hora de la anestesia. En casi un 20% de los pacientes, ocurrió un aumento de temperatura interna. Esto parece relacionarse con una temperatura corporal inicialmente baja. Las temperaturas internas durante la anestesia general eran mucho mayores en pacientes que habían recibido una mezcla de suxametonio y de halotano que en los a quienes se había administrado otras substancias. Esta observación posee un interés teórico y hace pensar que el aumento de temperatura en la hiperpirexia maligna puede constituir una exageración de la respuesta normal a dichos agentes.

Br. J. Anaesth. (1980), 52, 1231

BETA-ADRENERGIC BLOCKADE AND THE METABOLIC RESPONSE TO SURGERY

G. M. Cooper, J. L. Paterson, K. Mashiter and G. M. Hall

SUMMARY

The effect of the administration of propranolol 0.15 mg per kg body weight i.v. on the metabolic response to pelvic surgery was compared with results in similar patients who had not received propranolol. The only significant difference between the two groups was a lower plasma insulin concentration in the beta-blockade patients after 60 and 90 min of surgery. The glycaemic response to surgery was unimpaired in the propranolol-treated patients and there were no adverse haemodynamic effects. We conclude that β-adrenergic blockade is unlikely to have deleterious metabolic effects in healthy patients.

Propranolol was introduced into clinical practice in 1965 and since then β-adrenergic blocking drugs have been used with increasing frequency for the treatment of hypertension, angina and hyperthyroidism. For many years it was recommended that β-blocking drugs be discontinued before surgery, but recently Prys-Roberts and colleagues (1973) and Kopriva, Brown and Pappas (1978) have questioned the necessity and desirability of this policy. It is now common to find patients maintained on β-blocking drugs up to the time of surgery. Most of the studies on the interactions of β-blockade and anaesthesia have concentrated on the haemodynamic and myocardial effects. Since there have been several reports of hypoglycaemia associated with propranolol treatment (Kotler, Berman and Rubenstein, 1966; Mackintosh, 1967; Skinner and Misbin, 1976), we have investigated the metabolic effects of β-adrenergic blockade in patients undergoing gynaecological surgery.

PATIENTS AND METHODS

Twenty-four healthy women, admitted for Fallopian tube surgery, were investigated. They were allocated randomly to receive either propranolol 0.15 mg per kg body weight i.v. or an equivalent volume of saline. The nature of the study and the potential risks were explained to all patients before consent was obtained. The study was approved by the ethics committee of Hammersmith Hospital.

All patients were premedicated with papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. 1 h before surgery. On arrival in the anaesthetic room the duration of starvation before operation was determined and a central venous catheter was inserted percutaneously from an antecubital fossa to permit blood sampling and the administration of i.v. fluids and drugs. After the patient had rested for 15 min a control blood sample was collected and heart rate, arterial pressure and aural temperature measured. The calculated dose of propranolol, or an equivalent volume of 0.9% saline solution, was injected i.v. Fifteen minutes later another blood sample was collected and the physiological measurements repeated.

Anaesthesia was induced with sufficient thiopentone to abolish the eyelash reflex, the trachea was intubated following the administration of pancuronium and the lungs were ventilated with nitrous oxide in oxygen supplemented with 0.5% halothane using a Cape–Waine ventilator with a semi-closed circuit incorporating soda-lime. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.0–4.5% (Hartmann Braun URAS 4 infra-red carbon dioxide analyser) and an inspired oxygen concentration of 35–40% (Servomex DCL 101 Mk II oxygen analyser). The operating room temperature was maintained at 24 °C. Physiological saline solution was administered i.v. during surgery at approximately 6 ml kg^{-1} h^{-1}. Blood transfusion was not required as the measured blood loss did not exceed 150 ml.

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0007-0912/80/121231-06 $01.00

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Blood samples were collected at 30-min intervals during surgery and were analysed for glucose, glycerol, free fatty acids (FFA), lactate and alanine by methods described previously (Hall et al., 1980) and for insulin by radioimmunoassay using a human standard (WHO 66/304). The concentrations of each metabolite and insulin were estimated in duplicate and the coefficients of variation were: glucose 0.9%, glycerol 1.0%, FFA 1.2%, alanine 1.7%, lactate 3.8%, insulin 4.5%. At the same time as the blood sample was obtained the heart rate, arterial pressure and aural temperature were recorded (Holdcroft, Hall and Cooper, 1979).

On the 3rd day after operation the skinfold thicknesses of the patient were measured using skin calipers (John Bull, British Indicators Ltd) according to the method of Durnin and Rahaman (1974), and the percentage of fat to body weight calculated.

The results are expressed as mean values (±SEM). A two-way analysis of variance was used in both groups of patients to determine the presence of a significant change in mean concentration of substrate or hormone with time. A hierarchical two-way analysis of variance was performed, to assess the significance of any difference between the mean values of each group.

RESULTS

Details of the patients are shown in table I. The propranolol-treated patients were significantly fatter than the saline group ($P<0.05$).

TABLE I. *Details (mean ± SEM) of the two groups of patients. Significance of difference between means:* *$P<0.05$

	Saline ($n = 12$)	Propranolol ($n = 12$)
Age (yr)	31.3±0.7	30.7±0.9
Weight (kg)	59.8±1.8	63.0±1.8
Body fat (%)	26.6±1.5	31.7±0.9*
Duration of starvation (h)	16.0±0.7	15.0±0.9

The changes in heart rate, mean arterial pressure and aural temperature are shown in table II. In the saline group of patients there was a significant increase in heart rate after 30 min of surgery ($P<0.01$) but this was not maintained during the remainder of the operation. The administration of propranolol was associated with a marked decrease in heart rate from 87 to 59 beat min^{-1} before surgery ($P<0.01$). The onset of surgery caused an increase in heart rate in the propranolol-treated patients but the rates remained significantly less than the control value for the duration of surgery ($P<0.05$ and <0.01). Comparison between the two groups showed that there was a significantly slower heart rate in the β-blocked patients 15 min after the administration of propranolol and after 30 min of surgery ($P<0.05$), but thereafter the differences were not significant. Mean arterial pressure decreased slightly in both groups of patients, but this change was not significant. Aural temperature decreased significantly after 30 min of surgery in both groups ($P<0.01$) and this persisted for the duration of the study.

Changes in the concentrations of the metabolites and insulin are shown in table III. Both groups of patients showed the typical glycaemic response to surgery with an increase in blood glucose concentration from 3.94 to 5.08 mmol litre^{-1} in the saline group ($P<0.01$) and from 4.09 to 6.06 mmol litre^{-1} in the propranolol-treated patients ($P<0.01$). Plasma insulin values did not change significantly in the saline group, but were significantly decreased during surgery in the β-blocked patients ($P<0.01$). There was a significant difference between the insulin concentrations of the groups after 60 and 90 min of surgery ($P<0.05$). Blood lactate concentrations increased during surgery to 1.10 mmol litre^{-1} ($P<0.01$) in the saline group and to 1.11 mmol litre^{-1} ($P<0.05$) in the propranolol group. Plasma FFA and glycerol concentrations did not change significantly in the saline-treated patients, but in the β-blocked patients there were significant decreases in glycerol ($P<0.05$) and FFA ($P<0.01$ and <0.05) after 30 and 60 min of surgery. Blood alanine concentrations did not change significantly during this study.

DISCUSSION

The most important finding of this study was that β-adrenergic blockade had no adverse effects on the metabolic changes found during surgery. In particular the glycaemic response was normal and there was no evidence of hypoglycaemia in spite of 15 h starvation before operation. This is reassuring, as the cardiovascular response to hypoglycaemia is altered by propranolol with the occurrence of a bradycardia and hypertension (Lloyd-Mostyn and Oram, 1975), thus making hypoglycaemia even more difficult to detect under anaesthesia.

TABLE II. *Mean (±SEM) heart rate, mean arterial pressure, and aural temperature at the following times: S1 = control, S2 = 15 min after saline or propranolol, S3, S4, S5 and S6 = 30, 60, 90 and 120 min after commencement of surgery respectively. Significance of difference of means from S1 shown by* *$P<0.05$, ***$P<0.01$. *Differences between groups for each parameter shown in the final column. n.s. = not significant*

		S1	S2	S3	S4	S5	S6	Saline v. propranolol
Heart rate (beat min^{-1})	Saline	74.0±4.6	72.0±4.3	88.0±3.5**	79.0±3.7	71.0±2.4	69.0±2.4	$P<0.05$ at S2 and S3
	Propranolol	87.0±4.7	59.0±4.6**	76.0±3.0*	73.0±2.8*	69.0±2.6**	66.0±2.8**	
Mean arterial pressure (mm Hg)	Saline	92.0±3.1	92.0±2.6	89.0±2.6	88.0±2.0	87.0±2.6	87.0±3.5	n.s.
	Propranolol	94.0±1.9	88.0±2.2	87.0±2.4	86.0±2.0	87.0±2.0	85.0±3.4	
Temperature (°C)	Saline	36.5±0.07	36.5±0.07	36.0±0.11**	35.8±0.15**	35.9±0.15**	35.9±0.15**	n.s.
	Propranolol	36.4±0.09	36.5±0.10	36.0±0.13**	35.8±0.15**	35.7±0.16**	35.6±0.18**	

TABLE III *Mean (±SEM) concentrations of metabolites and insulin at the times indicated in table II. Significance of difference of means from control shown by* *$P<0.05$, ***$P<0.01$. *Differences between groups for each parameter shown in the final column. n.s. = not significant*

		S1	S2	S3	S4	S5	S6	Saline v. propranolol
Glucose (mmol litre^{-1})	Saline	3.94±0.15	4.04±0.16	3.90±0.26	4.83±0.20*	5.08±0.26**	4.86±0.17**	n.s.
	Propranolol	4.09±0.19	4.30±0.15	4.37±0.23	5.21±0.25**	5.27±0.36**	6.06±0.50**	
Insulin (mu. litre^{-1})	Saline	9.90±1.4	10.90±2.1	8.10±1.0	8.00±1.0	8.80±0.9	7.50±0.8	$P<0.05$ at S4 and S5
	Propranolol	10.90±0.7	9.30±0.8	6.50±0.6**	6.00±0.6**	6.30±0.7**	6.30±0.6**	
Alanine (µmol litre^{-1})	Saline	170±32	161±28	221±21	191±19	187±28	232±28	n.s.
	Propranolol	194±28	194±28	179 ±28	159±25	207±25	207±26	
Lactate (mmol litre^{-1})	Saline	0.64±0.08	0.57±0.08	0.72±0.10	1.07±0.10**	1.03±0.09**	1.10±0.08**	n.s.
	Propranolol	0.73±0.09	0.77±0.08	0.87±0.08	0.95±0.09	1.06±0.09*	1.11±0.14*	
FFA (mmol litre^{-1})	Saline	0.83±0.11	0.82±0.11	0.58±0.07	0.80±0.08	0.80±0.06	0.86±0.08	n.s.
	Propranolol	0.98±0.11	0.73±0.09	0.57±0.08**	0.66±0.07*	0.75±0.11	0.79±0.11	
Glycerol (µmol litre^{-1})	Saline	148±24	105±16	108±16	138±19	133±16	117±18	n.s.
	Propranolol	154±21	104±17	70±11*	92±14*	120±15	140±15	

One of the problems in assessing the metabolic effects of β-adrenergic blockade is the difficulty in quantifying the degree of blockade. The most common method is the construction of dose–response curves to isoprenaline with and without the β-adrenergic blocking drug (Vaughan Williams, Bagwell and Singh, 1973), but we considered this inappropriate in the present study both on ethical grounds and because of the effects of isoprenaline on metabolism. The administration i.v. of propranolol 0.15 mg kg^{-1} caused a marked decrease in heart rate from 87 to 59 beat min^{-1} after 15 min, but the rate increased when surgery began (table III). It is possible that this was a result of inadequate adrenergic blockade, but this is unlikely as the half-life of propranolol i.v. is 2–3.8 h (Shand, 1976). The most likely explanation for the increase in heart rate during surgery in propranolol-treated patients is the withdrawal of parasympathetic tone (Higgins, Vatner and Braunwald, 1973). Niarchos, Tahmooressi and Tarazi (1978) demonstrated that propranolol 10 mg i.v. abolished the isoprenaline-induced increase in heart rate but had only a limited effect on the tachycardia produced by changes in posture and the inhalation of amyl nitrate. Our results confirm the findings of Kopriva, Brown and Pappas (1978) that the heart rate response to surgery in patients anaesthetized with halothane is not a useful guide to the adequacy of β-adrenergic blockade, and suggest that the routine use of atropine in such patients, as advocated by Prys-Roberts and colleagues (1973), is unnecessary.

The failure of insulin secretion during surgery in the presence of an increased blood glucose concentration is well known (table III) and is thought to be the result of an increase in sympathetic activity in which α-adrenergic effects producing inhibition of insulin secretion predominate over the β-stimulatory effects (Allison, 1971). It is not surprising, therefore, that in the presence of propranolol the α-adrenergic inhibitory effects were even more pronounced with significantly lower plasma insulin concentrations after 60 and 90 min of surgery ($P < 0.05$) (table III). The lower plasma insulin values in the propranolol-treated patients were associated with a small increase in blood glucose concentration compared with the saline group. Basal insulin concentrations were not changed significantly by β-blockade, confirming the findings of other workers (Porte, 1967; Cerasi, Luft and Efendic, 1972; Robertson and Porte, 1973).

Day (1975) suggested that an important mechanism in the production of hypoglycaemia during β-adrenergic blockade was a decrease in the availability of gluconeogenic precursors. However, we failed to find any difference in the concentrations of three key gluconeogenic substrates, alanine, lactate and glycerol, between the two groups of patients (table III). The only gluconeogenic precursor to show an increase during surgery was lactate. We have observed a small but statistically significant increase in blood lactate concentration during surgery in other studies (Hall et al., 1978; Cooper et al., 1979) and the possible cause of this slight lacticacidaemia has been discussed previously (Cooper et al., 1979). It is probable, therefore, that hepatic glycogenolysis rather than gluconeogenesis makes the greater contribution to the increase in blood glucose concentration found during pelvic surgery. This may explain the failure of propranolol to affect the glycaemic response (table III) as the balance of the evidence suggests that catecholamine-mediated hepatic glycogenolysis occurs via stimulation of the α-adrenoreceptors (Syvalahti et al., 1977).

Many studies have demonstrated that β-blockade produces a significant decrease in plasma FFA values in various stressful states (for review see Day, 1975). Although the propanolol-treated patients had a significant reduction in plasma FFA and glycerol concentrations after 30 and 60 min of surgery, there was not a significant difference between the two groups of patients (table III). It is important to note, however, that the patients given propanolol were more obese than the saline group ($P < 0.05$, table I). Jung and colleagues (1979) have shown recently not only that obese subjects have higher basal FFA values than normal subjects but also that the lipolytic response to noradrenaline is greater in the obese. On this basis the patients in the β-blocked group have a greater adrenergically-mediated lipolytic response to surgery than the saline group and thus the effect of propranolol on plasma FFA and glycerol concentrations shown in table III is underestimated. This emphasizes the necessity of determining accurately the obesity of patients participating in metabolic studies.

In many patients, for example those with hypertension and coronary artery disease, there are haemodynamic benefits in maintaining β-adrenergic blockade up to the time of surgery and the results of the present study indicate that there are unlikely to be any severe metabolic problems. It must be emphasized, however, that we investigated young healthy women and it is unwise to extrapolate these findings to patients with abnormalities of glucose production and utilization, particularly diabetics, young children and septicaemic patients.

ACKNOWLEDGEMENTS

We thank Mr R. Winston for permission to study his patients and Miss A. Petrie for her invaluable statistical help.

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BLOCAGE BETA-ADRENERGIQUE ET LA REPONSE METABOLIQUE EN CHIRURGIE

RESUME

On compara l'effet de l'administration de 0,15 mg par kilo de poids corporel de propranolol i.v. sur la réponse métabolique à la chirurgie pelvique chez des patients analogues ayant ou non reçu du propranolol. La seule différence marquée entre les deux groupes consistait en une concentration d'insuline dans le plasma plus basse chez les patients soumis au blocage beta 60 et 90 min après l'opération. La réponse glycémique à la chirurgie ne fut pas altérée chez les patients ayant reçu un traitement beta-propranolol et on n'observa aucun effet hémodynamique adverse. On en tire la conclusion que le blocage beta-adrénergique ne produit vraisemblablement aucun effet métabolique nocif chez des patients sains.

BETA-ADRENERGISCHE BLOCKADE UND DIE REAKTION DES STOFFWECHSELS AUF DIE CHIRURGIE

ZUSAMMENFASSUNG

Die Wirkung einer intravenösen Verabreichung von Propanolol 0,15 mg pro kg Körpergewicht auf die Reaktion des Stoffwechsels auf Beckenchirurgie wurde mit den Ergebnissen bei Patienten verglichen, die kein Propranolol bekommen hatten. Der einzige bedeutende Unterschied zwischen den beiden Gruppen war eine niedrigere Plasmainsulinkonzentration bei den beta-blockierten Patienten 60 und 90 Minuten nach Anfang der Chirurgie. Die Blutzuckerspiegelreaktion auf die Chirurgie wurde bei den mit Propranolol behandelten Patienten nicht beeinträchtigt und es stellten sich auch keine nachteilige hämodynamische Wirkungen ein. Wir schliessen, dass eine ungünstige Auswirkung auf den Stoffwechsel bei gesunden Patienten infolge der beta-adrenergischen Blockade unwahrscheinlich ist.

EL BLOQUEO BETA-ADRENERGICO Y LA RESPUESTA METABOLICA A LA CIRUGIA

SUMARIO

Se comparó el efecto de la administración de 0,15 mg kg de propanolol por vía intravenosa sobre la respuesta metabólica a cirugía de la pelvis, con pacientes a los que no se les suministró propanolol. La única diferencia significativa entre los dos grupos fue una menor concentración de insulina en el plasma para aquellos pacientes con bloqueo-beta, después de 60 a 90 min de efectuada la operación. La respuesta glicémica no se imposibilitó en los pacientes tratados con propanolol y no se presentaron efectos hemodinámicos adversos. Consideramos, por lo tanto, que es bastante improbable que el bloqueo beta-adrenergico ejerza efectos nocivos en pacientes sanos.

Br. J. Anaesth. (1980), 52, 1237

CENTRAL HAEMODYNAMIC AND FOREARM VASCULAR EFFECTS OF MORPHINE IN PATIENTS AFTER OPEN HEART SURGERY

I. O. SAMUEL, J. D. MORRISON AND J. W. DUNDEE

SUMMARY

Central haemodynamic and forearm vascular changes following administration of morphine i.v. were studied in patients 24–30 h after open heart surgery. Right atrial pressure, heart rate, mean arterial pressure, cardiac output and stroke volume were measured before and after morphine 5 and 10 mg per 70 kg in 14 subjects. In a further group of eight subjects, forearm blood flow was measured after morphine 10 mg per 70 kg. Total systemic and forearm vascular resistance were derived from these measurements. In spite of wide individual variations, significant decreases in mean arterial pressure occurred in most of the patients and appeared to be dose related. Significant decreases in mean cardiac index were noted only after morphine 10 mg per 70 kg. Forearm blood flow increased consistently and significantly and there was a corresponding decrease in vascular resistance. The decrease in mean arterial pressure and the change in forearm vascular resistance indicated that vasodilatation was probably the principle cause of the decrease in arterial pressure, whereas the substained decrease in cardiac output seemed to indicate an effect on venous capacitance. The predominant action of morphine appears to be peripheral, causing a decrease in vascular resistance and, possibly, an increase in venous capacitance.

Opiates have been used in medicine since time immemorial and achieved a particular place in the treatment of patients acutely ill from trauma, burns, myocardial infarction and left ventricular failure, and in the relief of postoperative and other severe pain. More recently morphine has become popular as the main anaesthetic agent in open heart surgery. In spite of this there have been few documented studies of the haemodynamic effects of morphine in such patients (Fejfar et al., 1957; Thomas et al., 1965; Morrison et al., 1972). We have reported previously the effects of morphine in patients with normal cardiovascular function (Samuel, Clarke and Dundee, 1977) and report here similar studies of the haemodynamic effects of morphine in therapeutic dosage in patients with impaired cardiovascular function.

PATIENTS

Twenty-two patients with significant preoperative heart disease were studied 24–30 h after open heart surgery for valve replacement (table I). In all patients the heart rate and arterial pressure were stable and urinary output satisfactory. The trachea was intubated and ventilation of the lungs (40% oxygen in air) was assisted. Although all patients received opiates during the first 24 h following surgery for the relief of pain, no opiate drug had been given within the 4 h preceeding the study. In no patient was drug therapy required to maintain the circulation and there was no bleeding from the chest drains. Each patient had had radial artery and right and left atrial catheters placed at the time of operation, and these were still patent and available.

Since two distinct experimental programmes were followed each will be described separately with the results.

PART I: CENTRAL HAEMODYNAMICS

METHODS

Fourteen patients were studied. Arterial pressure (radial artery), right atrial pressure and the electrocardiogram were monitored continuously. Cardiac output was measured by the Hamilton–Stewart dye dilution method (Kinsman, Moore and Hamilton, 1929) using indocyanine green. The injection was made into the left atrium and blood was sampled from the radial artery. The results from computer analyses of the curves were confirmed by planimetry. At each determination of output the mean result from

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0007–0912/80/121237–10 $01.00

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TABLE I. *Details of patients. (*New York Heart Association)*

	Morphine (mg per 70 kg)	Mean age (yr)	Mean weight (kg)	Sex		NYHA Classification*	
				M	F	No. of patients	Class no.
Central haemodynamic studies						4	III
	5	54	67	2	4	2	IV
	10	47	59	3	5	4	III
						4	IV
Peripheral blood flow studies	10	51	61	6	2	4	III
						4	IV

TABLE II. *Average (±SEM) right atrial pressure, heart rate, total systemic vascular resistance, arterial pressure and cardiac index before and following morphine 5 mg per 70 kg.* *$P<0.005$

	Before morphine (control)	After morphine (min)		
		10	30	60
Right atrial pressure (mm Hg)	6.0 ±0.69	5.6 ±0.47	5.5 ±0.46	5.5 ±0.46
Heart rate (beat min^{-1})	106 ±3.6	104 ±2.9	104 ±2.4	104 ±2.4
Total systemic vascular resistance (mm Hg $litre^{-1}$ min^{-1})	39.6 ±1.12	39.7 ±2.58	42.3 ±3.95	41.8 ±2.66
Mean arterial pressure (mm Hg)	90 ±2.9	84* ±2.6	84* ±2.0	85 ±2.2
Cardiac index (litre min^{-1} m^{-2})	2.1 ±0.09	2.0 ±0.18	1.9 ±0.22	1.9 ±0.15
Stroke volume (ml)	36.6 ±1.91	32.2 ±1.97	37.0 ±2.94	37.5 ±1.56

two curves was used. From these direct measurements, the following indices were derived: mean arterial pressure (mm Hg) was calculated as the diastolic pressure plus one-third of the pulse pressure; total systemic vascular resistance (mm Hg $litre^{-1}$ min^{-1}) as the ratio of mean arterial pressure less central venous pressure, to cardiac output; cardiac index (litre min^{-1} min^{-2}) as the ratio of cardiac output to surface area and stroke volume (ml) as the ratio of cardiac output to heart rate. Once baseline values of arterial pressure, right atrial pressure and e.c.g. had been obtained (a), cardiac output was determined (b) and an arterial sample was withdrawn for analyses of blood-gas tensions (c). Morphine 5 mg per 70 kg (six patients) or 10 mg per 70 kg (eight patients) was injected via the right atrial catheter at the rate of 2 mg min^{-1} (d). The sequence of (a), (b) and (c) above, was repeated at 10, 30 and 60 min after the injection of morphine.

RESULTS

Morphine 5 mg per 70 kg (tables II and III)

The individual changes in right atrial pressure following the administration of morphine were never greater than 2 mm Hg and there was no significant difference in the mean values obtained before and after the administration of morphine. Although heart rate decreased by 8 beat min^{-1} in one patient the mean difference was not significant at any time. Mean arterial pressure decreased in five of the six subjects, the average decrease being from 90 mm Hg (control) to 84 mm Hg at 10 min and to 85 mm Hg at 60 min. This change was statistically significant at 10 ($P<0.005$) and 30 ($P<0.005$) min. There was no consistent corre-

TABLE III. *Individual changes in haemodynamic variables in six patients, at 10 min, and average changes at 10, 30 and 60 min following morphine 5 mg per 70 kg.* + = *increase;* − = *decrease*

	10 min							30 min	60 min
Subject:	1	2	3	4	5	6	(Mean)	(Mean)	(Mean)
Right atrial pressure (mm Hg)	0	0	+0.4	0	−1.5	−1.5	−0.4	−0.5	0.0
Heart rate (beat min^{-1})	0	−4	+2	−8	0	+2	−1.3	−1.7	−1.7
Total systemic vascular resistance (mm Hg litre^{-1} min^{-1})	−9.1	+7.5	−0.1	+2.1	−3.0	+3.5	+0.16	+3.0	+2.2
Mean arterial pressure (mm Hg)	−10	−4	−6	0	−6	−8	−6	−6	−5
Cardiac index (litre min^{-1} m^{-2})	+0.34	−0.36	−0.17	−0.13	+0.06	−0.33	−0.09	−0.16	−0.18
%Change	+15	−20	−8	−6	+3	−18	−5	−11	−11
Stroke volume (ml)	−1.5	+4.6	+3.8	+8.9	−0.9	+7.7	−4.0	+0.4	+1.0

TABLE IV. *Average (±SEM) right atrial pressure, heart rate, total systemic vascular resistance, mean arterial pressure and cardiac index before and following morphine 10 mg per 70 kg.* $^{*}P < 0.05$; $^{**}P < 0.025$

	Before morphine (control)	After morphine (min)		
		10	30	60
Right atrial pressure (mm Hg)	6.5 ±0.38	6.8 ±0.25	6.7 ±0.26	6.7 ±0.26
Heart rate (beat min^{-1})	107 ±2.2	104 ±2.6	102 ±1.3	102 ±1.3
Total systemic vascular resistance (mm Hg litre^{-1} min^{-1})	43.3 ±3.46	46.4 ±3.26	46.7 ±3.06	47.4 ±4.12
Mean arterial pressure (mm Hg)	93 ±2.1	83** ±4.4	85** ±2.9	89 ±2.1
Cardiac index (litre min^{-1} m^{-2})	2.0 ±0.14	1.7** ±0.14	1.7* ±0.11	1.8 ±0.15
Stroke volume (ml)	32.5 ±2.06	26.7** ±2.49	32.3 ±1.95	32.9 ±2.73

lation between the changes in mean arterial pressure and heart rate in individual patients. Total systemic vascular resistance increased in three subjects, decreased in two and was practically unaltered in the other. However, when the differences were measured no statistical significance emerged. Cardiac index (fig. 1) had decreased in five of the six patients at 10 min, in two instances by approximately 20%, whilst it increased by 15% in the sixth patient. There was no consistent relationship with arterial pressure. Indeed, the one patient in whom the cardiac output increased had the greatest decrease in mean arterial pressure. Changes at 30 min were similar with a return to near baseline values by 60 min. Although individual patients showed marked changes, the differences between the means in the groups were not significant.

Morphine 10 mg per 70 kg (tables IV and V)

The individual changes in right atrial pressure were never greater than 2 mm Hg and there was no

TABLE V. *Individual changes in haemodynamic variables in eight patients at 10 min and average changes at 10, 30 and 60 min following morphine 10 mg per 70 kg. + = increase; − = decrease*

	10 min									30 min	60 min
Subjects:	1	2	3	4	5	6	7	8	(Mean)	(Mean)	(Mean)
Right atrial pressure (mm Hg)	0	0	+1.5	−0.4	0	0	+0.4	0	+0.2	+0.1	+0.1
Heart rate (beat min^{-1})	0	+10	−12	+4	−12	+2	0	−2	−3	−4	−4
Total systemic vascular resistance (mm Hg $litre^{-1}$ min^{-1})	−7.9	+12.2	−7.5	−0.1	+18.1	−1.6	+0.3	−0.6	+3.1	+3.4	+4.1
Mean arterial pressure (mm Hg)	0	−22	−20	−4	0	−12	−20	−10	−10	−8	−4
Cardiac index (litre min^{-1} m^{-2})	+0.31	−0.87	−0.17	−0.06	−0.60	−0.47	−0.48	−0.47	−0.35	−0.35	−0.22
% Change	−21	−47	−8	−4	−30	−17	−23	−21	−20	−20	−10
Stroke volume (ml)	−2.3	+14.2	+1.6	+1.0	+5.8	+7.2	+11.6	+6.8	−5.7	−0.2	+0.5

significant difference in the mean values for the group. Heart rate decreased by 12 beat min^{-1} in two patients, increased by 10 beat min^{-1} in one patient and was practically unaltered in the other patients. The mean difference was not significant at any time. Mean arterial pressure decreased in five of eight subjects, the average decrease being from 93 mm Hg (control) to 83 mm Hg at 10 min and to 89 mm Hg at 60 min. The magnitude of the change was greater than that seen after morphine 5 mg per 70 kg and the average decrease was significant at 10 ($P<0.025$) and 30($P<0.025$) min. There was no consistent correlation with the changes in heart rate. Peripheral vascular resistance increased in two subjects, decreased in two and was practically unaltered in the others. There was no significant difference in mean values before and after the injection of morphine. Ten minutes after the administration of morphine, cardiac index (fig. 1) had decreased in all but one patient, and in five patients the decrease was greater than 20% of the baseline values. In one patient it increased by about 20%. Although no consistent relationship with arterial pressure was seen mean arterial pressure decreased by more than 10 mm Hg in the majority of the patients. The decrease in cardiac index persisted for 30 min with some return towards control values at 60 min. The differences between the means in this group were significant at 10 ($P<0.05$) and 30 ($P<0.025$) min.

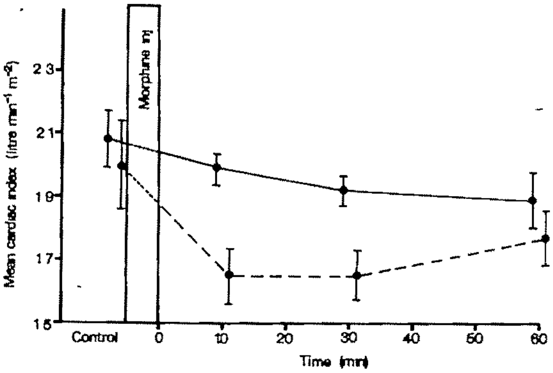

FIG. 1. Changes in mean cardiac index (litre min^{-1} m^{-2}) after the administration of morphine 5 mg per 70 kg (——) or 10 mg per 70 kg (---) i.v.

Blood-gas analysis (table VI).

There were no significant differences in Pa_{O_2}, Pa_{CO_2} and standard bicarbonate concentration at any time. The patients remained normocapnic throughout and the high Pa_{O_2} values reflect merely the increased FI_{O_2} while on assisted ventilation.

PART II: FOREARM BLOOD FLOW STUDIES

METHODS

Eight patients were studied as follows: intra-arterial pressure was monitored continuously and

TABLE VI. *Effect of morphine 5 and 10 mg on arterial blood-gas tensions and standard bicarbonate concentration ($F_{I_{O_2}}$ = 0.4). n.s. = not significant*

	Dose of morphine (mg)	Before morphine (control)	After morphine (min)		
			10	30	60
Mean standard bicarbonate (mmol litre $^{-1}$)	5	25.5 ±0.48	23.7 ±0.43 n.s.	24.8 ±0.36 n.s.	25.0 ±0.39 n.s.
	10	24.8 ±1.12	24.3 ±0.89 n.s.	23.7 ±0.77 n.s.	24.1 ±0.76 n.s.
Mean Pa_{O_2} (kPa)	5	19.2 ±0.51	20.3 ±0.49 n.s.	19.4 ±0.46 n.s.	19.8 ±0.49 n.s.
	10	19.4 ±0.49	19.1 ±0.51 n.s.	19.7 ±0.51 n.s.	18.9 ±0.48 n.s.
Mean Pa_{CO_2} (kPa)	5	5.2 ±0.09	5.0 ±0.12 n.s.	5.2 ±0.10 n.s.	5.1 ±0.19 n.s.
	10	4.8 ±0.05	4.9 ±0.04 n.s.	4.8 ±0.06 n.s.	5.0 ±0.06 n.s.

forearm blood flow was determined by venous occlusion plethysmography, using a mercury-filled rubber strain gauge (Whitney, 1953). Flow records were obtained three times a minute, and each value shown is the average of six measurements, expressed as ml per dl forearm volume per minute. From these direct measurements, the following indices were derived: mean arterial pressure (mm Hg) and forearm vascular resistance (resistance units) (the ratio of mean arterial pressure to forearm blood flow).

The experimental programme was as follows: the collecting cuff was inflated to a pressure of 200 mm Hg; control recordings of forearm blood flow and arterial pressure were made until a "steady state" was obtained—usually in about 20 min; morphine 10 mg per 70 kg was injected via a right atrial catheter at the rate of 2 mg min^{-1} and forearm blood flow and arterial pressure were recorded at 20-s intervals for 20 min from the end of the injection of morphine. Forearm blood flow and arterial pressure were measured also 30, 40, 50 and 60 min after the injection. In order to rest the arm, the collecting cuff was deflated for 5 min after the 20- and 40-min readings and re-inflated to the original pressure at least 1 min before commencement of subsequent measurements of forearm blood flow.

Each patient acted as his own control and the subsequent paired data were available for statistical analysis by Student's t test.

RESULTS

Morphine 10 mg per 70 kg

The most notable feature was the low resting forearm blood flow, the average values being 2.6 ml per dl forearm volume per minute (table VII). Increases in forearm blood flow were observed 2 min after the end of the morphine injection in some patients (1, 4, 5) while in three patients (2, 3, 7) this response was not seen until 16–30 min. However, in mean values there was a statistically significant increase at 4 min ($P < 0.05$) while the peak increase occurred at 20 min.

Decreases occurred in mean arterial pressure in most patients but in two (2.7) there was no change. The extent of the decrease was variable, unpredictable and of the same order as had been observed previously in the central haemodynamic study. However, a good correlation between the degree of hypotension and increase in forearm blood flow was obtained. Decreases in mean values of forearm vascular resistance ($P < 0.025$) were observed as early as 2 min from the end of the injection of morphine, the peak effect occurring at 20 min (table VIII). Even at the end of 60 min, the forearm vascular resistance remained decreased ($P < 0.025$).

TABLE VII. *Measurements of forearm blood flow (ml min^{-1} per dl forearm volume) at intervals after injection of morphine 10 mg per 70 kg i.v. Each value is an average of six measurements*

Patient no.	Control	Time after injection (min)													
		2	4	6	8	10	12	14	16	18	20	30	40	50	60
1	2.3	2.5	2.6	3.0	3.1	3.1	3.2	3.2	3.2	3.2	3.3	3.2	3.2	3.0	3.0
2	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.6	2.7	2.8	2.9	2.8	2.8
3	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.9	2.9	2.9	3.0	3.0	3.0	3.0
4	1.9	2.0	2.3	2.3	2.5	2.5	2.6	2.6	2.7	2.7	2.9	2.8	2.7	2.3	2.3
5	2.0	2.1	2.3	2.5	2.6	2.8	2.8	2.8	2.8	2.9	3.1	3.0	3.1	3.0	3.0
6	3.2	3.2	3.3	3.2	3.3	3.4	3.4	3.7	3.8	3.7	3.7	3.4	3.2	3.2	3.2
7	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	3.0	3.0	3.0	2.9
8	3.3	3.3	3.3	3.5	3.6	3.6	3.6	3.7	3.8	3.8	3.8	3.8	3.6	3.3	3.3
Mean	2.6	2.7	2.8	2.9	2.9	3.0	3.0	3.1	3.1	3.1	3.2	3.1	3.1	3.0	2.9
SEM	0.19	0.17	0.14	0.13	0.13	0.14	0.13	0.15	0.16	0.16	0.14	0.12	0.09	0.11	0.11

TABLE VIII. *Measurements of forearm vascular resistance (resistance unit) at intervals after injection of morphine 10 mg per 70 kg i.v. Each value is an average of six measurements*

Patient no.	Control	Time after injection (min)													
		2	4	6	8	10	12	14	16	18	20	30	40	50	60
1	34.8	28.0	26.9	20.0	19.4	19.4	18.8	18.8	20.3	18.8	19.7	21.9	21.9	23.3	23.3
2	33.3	33.3	33.3	33.3	33.3	33.3	33.3	33.3	33.3	34.6	33.3	32.1	31.0	32.1	32.1
3	26.8	26.8	26.8	26.8	25.0	25.0	25.0	25.0	24.1	25.9	25.9	25.0	25.0	25.0	25.0
4	42.1	37.5	30.4	30.4	26.0	26.0	25.0	25.0	24.1	24.1	22.4	25.0	27.8	34.8	34.8
5	42.5	40.5	34.8	32.0	26.9	25.0	23.2	23.2	25.0	24.1	22.6	23.3	24.2	25.0	25.0
6	28.1	26.6	25.8	26.6	25.8	25.0	25.0	23.0	22.4	23.0	23.0	25.0	26.6	26.6	26.6
7	27.6	27.6	27.6	27.6	27.6	27.6	27.6	27.6	27.6	27.6	27.6	26.7	26.7	26.7	27.6
8	22.7	21.2	21.2	20.0	19.4	19.4	19.4	20.3	19.7	19.7	18.4	18.4	19.4	21.2	21.2
Mean	32.2	30.2	28.4	27.1	25.4	25.1	24.7	24.5	24.6	24.7	24.1	24.7	25.3	26.8	27.0
SEM	2.57	2.26	1.54	1.77	1.59	1.58	1.62	1.59	1.54	1.75	1.68	1.39	1.27	1.59	1.60

DISCUSSION

A clear pharmacodynamic interpretation of the results is difficult. The patients were not a homogeneous group, and variables such as the extent of the pre-existing myocardial disease, the haemodynamic and metabolic sequelae of surgery and cardiopulmonary bypass, the level of sympathetic activity, and alteration in vascular capacity are all likely to have influenced the results. However, because individual patients acted as their own controls, while other factors remained the same, the changes seen with morphine must be attributed to the drug itself, although this does not imply necessarily that exactly similar mechanisms were operating in each individual, and it is not surprising that there was a considerable degree of variability in the individual responses. Nonetheless, dominant trends did emerge. The administration of morphine was followed by decreases in arterial pressure and cardiac index, with little change in central venous pressure and systemic vascular resistance, whilst plethysmography in a comparable group of patients showed a consistent decrease in vascular resistance and a corresponding increase in flow. Similar studies in patients with normal cardiovascular function showed the decrease in arterial pressure, but no significant changes in cardiac output or central venous pressure (Samuel, Clarke and Dundee, 1977).

If respiratory depression is eliminated, the effects of morphine on the cardiovascular system are likely to be mediated through a central nervous system mechanism, by direct myocardial depression, by a direct effect on the peripheral vasculature, or by a combination of these.

Central effects

Depression of the vasomotor centre, although thought to be an important cause of the hypotension following morphine, is now accepted generally as being of little importance following clinically used doses (Jaffe, 1965). Certainly bradycardia was not a feature of the hypotension which occurred in these patients.

Relief of pain, mental sedation and sleep follow the therapeutic use of morphine and it could be argued that the haemodynamic changes seen in these patients represented little more than the reduction of sympathetic activity, secondary to relief of discomfort and anxiety. However, the patients did not go to sleep during these studies nor did they show clinical evidence of being in pain, physical discomfort or anxiety before the administration of morphine. There is considerable supporting evidence in man that the peripheral vascular effects of morphine are not mediated via the sympathetic system for, not only are such effects unaltered in the sympathectomized or nerve-blocked limbs, but they are not blocked by naloxone which is assumed to block all central nervous system morphine receptors (Johnstone et al., 1974; Samuel and Dundee, 1975).

Myocardial depression

All patients in the present study had chronic valve lesions associated with significant impairment of activity before operation, objective evidence of which included the low resting cardiac indices (mean 2 litre min^{-1} m^{-2}) and a decrease in mean stroke volume (32.5 ml). These values are similar to those given by Wade and Bishop (1962) and Kelman (1971) for patients with chronic heart failure.

Wisheart (1975) observed that, early after cardiopulmonary bypass, there are important changes in myocardial performance, not only from normality but also from the individual's preoperative status. The more important included abnormalities of the autoregulatory mechanism for control of the coronary circulation, oedema of the myocardium and increased oxygen consumption. Under these conditions it is likely that any additional stress which tends to increase myocardial oxygen demand may exceed the ability of the coronary circulation to provide it. Although in this series of investigations the cardiac output decreased, the central venous pressure did not increase correspondingly, so that there was no direct evidence of a decrease in myocardial contractility. However, left atrial pressure was not measured and could have increased independently of the right-sided pressures. In addition, the decrease in arterial pressure seen in this study would have evoked normally a baroreceptor reflex, but evidence of this was not seen. Therefore it is impossible from the present data to exclude fully a direct depressant effect of morphine on either myocardial contractility or the homeostatic mechanisms of the diseased heart. However, it should be noted that a primary myocardial depressant effect from morphine has not been demonstrated either in isolated myocardial tissue or in a heart–lung preparation (Huggins, Glass and Bryan, 1951; Strauer, 1972).

Forearm vascular changes

Among the most consistently reported effects of morphine is that of peripheral vascular dilatation (Zelis et al, 1974; Samuel, Unni and Dundee, 1977; Hsu, Hickey and Forbes, 1979) and an increase in venous capacitance. In the present study a consistent decrease in vascular resistance and increase in forearm blood flow were seen.

Although the diseased heart is unable to provide a normal cardiac output, there is often an almost normal arterial pressure. This is achieved by an increase in peripheral vascular resistance, albeit at the cost of a decrease in tissue perfusion. Ferrer and his colleagues (1965) found that splanchnic blood flow was reduced in chronic heart failure by roughly the same proportion as was cardiac output, whilst Donald, Bishop and Wade (1955) found that resting arm blood flow was decreased markedly in patients with heart disease and that there was a good correlation between the local decrease in blood flow and the reduction in cardiac output. The present group of patients was no exception, having low resting forearm flows with a sustained increase in resting vascular resistance, presumably a result, at least in part, of an increase in sympathetic tone. Patients with long-standing heart disease have decreased vasodilator responses (Heistad and Abboud, 1974) and Zelis, Mason and Braunwald (1968) have shown that the forearm vessels in such patients failed to dilate normally in response to physiological stimuli such as ischaemia, excercise and pyrexia. Nonetheless, in spite of the low resting flow, the vasodilator response to morphine in our group was unaffected, being comparable to the changes seen in patients with normal cardiovascular function (Samuel, Unni and Dundee, 1977). Indeed, the relationship between the decrease in mean arterial pressure and change in forearm vascular resistance indicates that vasodilatation was probably a principal cause of the early decrease in arterial pressure which occurred after the administration of morphine.

However, the maximum effect on peripheral blood flow and resistance was seen 20 min after injection, while the decrease in arterial pressure and cardiac output in the comparable group of patients in Part I of the study was still evident after 1 h. This may be indirect evidence of an effect on venous capacitance outlasting the effect on the resistance vessels (Hsu, Hickey and Forbes, 1979).

While there is little dispute that morphine causes peripheral vasodilatation, there has been considerable speculation as to the precise mechanism underlying this action. The possibilities are of a neurally mediated effect, a humoral effect, a direct effect or some combination of these. Amongst these, a "direct action" has been shown to be the most important mechanism operating in pain-free individuals (Zelis et al., 1974; Samuel, Unni and Dundee, 1977).

However, it is surprising that, while the majority of patients in Part II of the study showed a consistent decrease in forearm vascular resistance, the total systemic vascular resistance remained remarkably unchanged. Therefore, it could be assumed that a compensatory vasoconstriction must have occurred simultaneously in some other part of the body, possibly in the portal or splanchnic vascular system. Such regional differences in vascular response to morphine have been evident in animals (Schmidt and Livingston, 1933) but have not been studied in man.

Since the decrease in forearm vascular resistance was such a consistent finding in the patients in Part II, why was such variability and unpredictability seen in the central haemodynamic measurements in the comparable group of patients in Part I? The evidence would suggest that the answer be sought in the patients' circulatory volume at the time of study. In 1946, Drew, Dripps and Comroe demonstrated that healthy subjects developed orthostatic hypotension when morphine was given in the upright position, but that this could be reduced by bandaging the legs. Thomas and colleagues (1965) found that morphine caused hypotension in some patients with acute myocardial infarction and that this was reversible by raising the legs, again suggesting that peripheral pooling of blood was responsible for the hypotension. In the report by Morrison and co-workers (1972) of measurements of central haemodynamics soon after the end of cardiopulmonary bypass, it was inferred that suboptimal blood volume may have been responsible for the wide variation in the haemodynamic response. Therefore, the present investigation was timed deliberately at 24–30 h after the end of surgery, by which time a more stable haemodynamic and hydrodynamic state would be anticipated. In spite of this, the results of this study showed the same type of unpredictability and variation, although the mean changes in arterial pressure and cardiac output revealed a clearer trend towards decreases from control values. Lowenstein and co-workers (1969) suggested that the net effect of morphine on the circulation of human subjects may depend partially on the circulating blood volume. It seems likely that the same holds true in these patients with impaired cardiovascular function, where the circulating blood volume is balanced more critically than in normal subjects.

Therefore, it appears that the net effect of the administration of morphine is to decrease peripheral vascular resistance and increase venous capacitance, resulting in a reduction in both peripheral resistance and effective circulating blood volume. This produces decreases in arterial pressure and cardiac output in patients with decreased cardiac reserve who have a limited capacity to compensate.

ACKNOWLEDGEMENTS

We wish to thank Messrs J. C. Cleland and H. O. O'Kane, Consultant Cardiac Surgeons, for permitting us access to their patients. We also wish to thank our colleagues in the cardiac recovery ward of the Royal Victoria Hospital, Belfast, for their co-operation. Dr I. O. Samuel is grateful to the Eastern Health and Social Services Board for a research grant from the endowment funds of the Royal Victoria Hospital which enabled him to carry out this work.

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EFFETS VASCULAIRES SUR L'AVANT-BRAS ET EFFETS HEMODYNAMIQUES CENTRAUX DE LA MORPHINE CHEZ DES PATIENTS AYANT SUBI DES OPERATIONS A COEUR OUVERT

RESUME

On procéda à l'étude des changements vasculaires de l'avant-bras ainsi que des effets hémodynamiques centraux chez des patients auxquels on avait administré de la morphine i.v. 24–30 h après des opérations à coeur ouvert. Chez 14 sujets auxquels on avait administré 5 et 10 mg de morphine par 70 kg, on mesura avant et après, l'administration de la substance la pression atriale droite, le rythme cardiaque, la pression artérielle moyenne, le débit cardiaque et le volume systolique. Chez un autre groupe de huit sujets, on mesura le flux sanguin de l'avant-bras après avoir administré 10 mg de morphine par 70 kg. A partir de ces valeurs, on a obtenu la résistance vasculaire de l'avant-bras et la résistance systémique totale. En dépit de grandes variations individuelles, des baisses significatives de la pression artérielle moyenne qui semblaient découler de l'importance du dosage se sont produites chez la plupart des patients. On n'observa de baisses significatives de l'index cardiaque moyen qu'après l'administration de 10 mg de morphine par 70 kg. Le flux sanguin de l'avant-bras augmenta de façon continue et significative et s'accompagne d'une baisse correspondante de la résistance vasculaire. La baisse de pression artérielle moyenne et le changement intervenu dans la résistance vasculaire de l'avant-bras démontrèrent que la vasodilatation constituait vraisemblablement la cause principale de la baisse de pression artérielle, tandis qu'une diminution continue du débit cardiaque semble indiquer un effet sur la capacitance veineuse. L'action prédominante de la morphine semble être périphérique et provoquer une baisse de la résistance vasculaire ainsi qu'une augmentation possible de la capacitance veineuse.

ZENTRALE HÄMODYNAMISCHE UND VORDERARM-VASKULÄRE AUSWIRKUNGEN VON MORPHIN NACH OFFENHERZCHIRURGIE

ZUSAMMENFASSUNG

Zentrale hämodynamische und vorderarm-vaskuläre Änderungen nach intravenöser Verabreichung von Morphin wurden 24–30 Stunden nach Offenherzchirurgie studiert. Rechter Vorhofdruck, Herzschlage pro Minute, durchschnittlicher arterieller Druck, Herzminutenvolumen und Schlagvolumen wurden vor und nach Morphin 5 und 10 mg pro 70 kg bei 14 Patienten gemessen. In einer weiteren Gruppe von 8 Patienten wurde der Blutfluss im Vorderarm nach Morphin 10 mg pro 70 kg gemessen. Der Gefässwiderstand des Gesamtsystems und der vorderarmvaskuläre Widerstand wurde von diesen Werten abgeleitet. Trotz weitgehender Variationen traten bei den meisten Patienten bedeutende Verminderungen des durchschnittlichen Arteriendrucks auf, die anscheinend dosisabhängig waren. Bedeutende Verminderungen des durchschnittlichen Herzindex wurden schon nach 10 mg pro 70 kg beobachtet. Der Blutfluss im Vorderarm nahm bedeutend und konsequent zu und der Gefässwiderstand nahm entsprechend ab. Die Verminderung des durchschnittlichen Arteriendrucks und die Änderung bei dem Gefässwiderstand des Vorderarms deuteten an, dass die

Verminderung des Arteriendrucks wahrscheinlich hauptsächlich auf eine Gefässerweiterung zurückzuführen war, während die anhaltende Verminderung des Herzminutenvolumens eine Wirkung auf die Venenkapazität anzudeuten schien. Die Hauptwirkung von Morphin scheint peripher zu sein, wobei eine Verminderung des Gefässwiderstandes und eventuell eine Vergrösserung der Venenkapazität herbeigeführt werden.

EFECTO DE LA MORFINA EN EL SISTEMA VASCULAR DEL ANTEBRAZO Y EN EL SISTEMA HEMODINAMICO CENTRAL DE PACIENTES SOMETIDOS A CIRUGIA A CORAZON ABIERTO

SUMARIO

En pacientes sometidos a cirugía a corazón abierto se les administró morfina intravenosa, de 24 a 30 h después de la operación, estudiándose los cambios en el sistema vascular del antebrazo y el sistema hemodinámico central. Se midieron en 14 pacientes la presión atrial derecha, el rítmo cardiaco, la presión media arterial, la potencia cardiaca y el volumen de la expulsión, antes y después de la inyección de 5 mg y de 10 mg de morfina/70 kg. En otro grupo de 8 pacientes se midió el flujo sanguíneo del antebrazo después de 10 mg de morfina/70 kg. De estas mediciones se derivó la resistencia vascular del antebrazo y la resistencia sistemática total. A pesar de las enormes variaciones que se presentan a nivel individual, tuvieron lugar disminuciones significativas de la presión media arterial en la mayoría de los pacientes y al parecer dichas disminuciones van en relación a la dosis. Se apreciaron disminuciones significativas en el indice cardiaco medio después de tan sólo 10 mg de morfina/70 kg. El flujo sanguíneo en el antebrazo incrementó de forma consistente y significativa y tuvo lugar una disminución correspondiente de la resistencia vascular. La disminución en la presión media arterial y el cambio en la resistencia vascular del antebrazo indicaron que probablemente la causa principal de la disminución de la presión arterial fue la vasodilatación, mientras que la constante disminución de la producción cardiaca parece indicar un cierto efecto sobre la capacidad venosa. La acción predominante de la morfina parece ser de caracter periférico, causando una disminución de la resistencia vascular y, posiblemente, un incremento de la capacidad venosa.

Br. J. Anaesth. (1980), 52, 1247

EFFECT OF ORAL BENZODIAZEPINES ON MEMORY

A. C. McKay and J. W. Dundee

SUMMARY

The effects of the oral administration of diazepam 5, 10 and 20 mg, flunitrazepam 0.5 and 1 mg and lorazepam 1, 2 and 4 mg on memory were studied in groups of healthy patients before surgery. The degree of sedation was noted also. A dose-related amnesic effect was produced by all the drugs, but this was not significant with diazepam 5 mg and lorazepam 1 mg. Larger doses of diazepam (10 and 20 mg) produced brief amnesia comparable to equivalent doses of flunitrazepam (0.5 and 1 mg). There was the same delay in the onset of amnesia after oral lorazepam 4 mg as when it was given i.v. and its effect lasted for at least 90 min after administration. In contrast to the effect of the same drugs given i.v., drowsiness and failure of recognition follow a similar time course.

Shortly after its introduction it was noted that i.v. diazepam caused anterograde amnesia (Brandt and Oakes, 1965; Haslett and Dundee, 1968). This property has since been investigated in a number of clinical studies. The amnesic action is more marked when diazepam is given i.v. than after i.m. injection (Pandit and Dundee, 1970; Pandit, Dundee and Keilty, 1971). The latter authors found that narcotic analgesics given alone produced a negligible frequency of amnesia, but caused more drowsiness after operation than combinations of diazepam or hyoscine and suggested a specific amnesic action of diazepam. Dundee and Pandit (1972) found that diazepam 10 mg i.v. caused significantly more amnesia than hyoscine 0.4 mg or 0.6 mg, the peak effect of diazepam occurring 2–3 min after administration and lasting 20–30 min. Frumin, Herekar and Jarvik (1976) also found diazepam to be more effective than hyoscine, although their stimuli were not presented until 15 min after i.v. injection.

Clarke and others (1970), in a detailed volunteer study, confirmed that i.v. diazepam, in clinical doses, caused anterograde amnesia maximal in the first 10 min after administration and that this was not accompanied by a serious reduction in the level of consciousness. They concluded that the drug acts upon the process of consolidation in memory formation rather than registration (input) or retrieval (output) (fig. 1). This was also the finding of Grove-White and Kelman (1971) and of Gregg, Ryan and Levin (1974). These latter authors also noted, in patients undergoing oral surgery under local anaesthesia and i.v. diazepam, that "strong" operative stimuli were recalled more frequently than experimental stimuli, and that these two responses paralleled each other. Ghoneim and Mewaldt (1975) reached similar conclusions on the mode of action of both diazepam and hyoscine and suggested that a central anticholinergic action might be involved in both cases.

Amnesic properties have also been attributed to the more recently introduced benzodiazepine, lorazepam, even when given by mouth (Wilson and Ellis, 1973; Harry and Richards, 1972). With the i.v. route, Heisterkamp and Cohen (1975), using a single stimulus presented 30 min after injection, found a dose-related amnesic effect with lorazepam, but no significant amnesia with diazepam or pentobarbitone. Other authors have also found marked amnesia with i.v. lorazepam (Blitt et al., 1976; Taub and Eisenberg, 1976; George and Dundee, 1977; Brown et al., 1978). Flunitrazepam (R05 4200; Rohypnol) also causes anterograde amnesia (Dundee et al., 1976), comparable in effect, in terms of both the extent and duration of action, to that of equivalent doses of diazepam (George and Dundee, 1977).

It appears to be a consistent finding that, in adequate doses, i.v. diazepam causes rapid onset (2–3 min), short-lasting (20–30 min) anterograde amnesia. Increasing the dose affects the duration rather than the degree of amnesia (Gregg, Ryan and Levin, 1974; Dundee, 1979). In contrast, lorazepam has an amnesic action after both oral and i.v. administration; with both routes there is a

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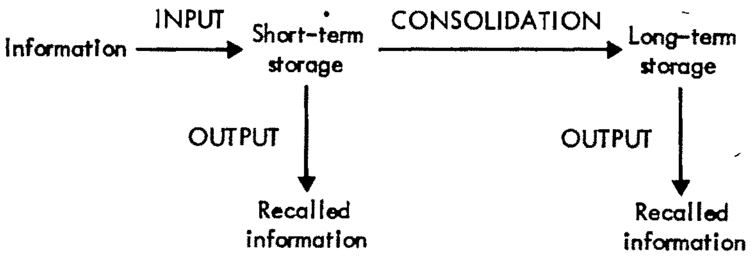

FIG. 1. Suggested model of memory processes (Cherkin and Harroun, 1971).

delay in onset (30–40 min) and prolonged amnesia (up to 270 min). The findings for oral diazepam are less consistent, however. Several authors did not find amnesia (Dundee and Keilty, 1969; Harry and Richards, 1972; Wilson and Ellis, 1973), although it was reported in volunteers by Baird and Hailey (1972).

Although the amnesic properties of i.v. benzodiazepines are important, clinically, the popularity of the drugs in routine premedication depends largely on the ease and convenience of their oral administration. Evidence on their amnesic action by this route is conflicting. The present study was carried out in an attempt to quantify this using the method of Dundee and Pandit (1972), Dundee and George (1976) and George and Dundee (1977) as described for i.v. drugs. In addition, an attempt was made to investigate any relationship between amnesia and sedation and to ascertain to what extent these properties are separate entities.

TABLE I. *Details and numbers of patients in the various groups studied*

Drug	Dose (mg)	Mean age (yr)	Mean weight (kg)	*n*
Diazepam	5	31	61	10
Diazepam	10	31	60	20
Diazepam	20	29	59	20
Flunitrazepam	0.5	33	59	20
Flunitrazepam	1	30	58	20
Lorazepam	1	29	62	20
Lorazepam	2	31	58	10
Lorazepam	4	29	58	20
Lorazepam + hyoscine	2 1	32	58	10
Lorazepam + hyoscine	4 1	33	63	10
Inert		30	57	40

PATIENTS AND METHODS

The investigations were carried out on healthy adult women, weighing between 45 and 75 kg, about to undergo minor gynaecological operations. They were not receiving any regular medication and had not been given any drugs on the night before surgery. Each drug or combination of drugs was studied in not less than 10 patients (table I).

A simplified, standard explanation of the nature and purpose of the study was given to each patient and verbal permission to participate was obtained. The patient was shown a familiar object such as a pen, and asked to identify it and the test drug was administered (fig. 2).

Five minutes after administration the patient was shown a picture postcard of a familiar scene and asked to identify it without prompting or correction. A second card was shown 5 min later

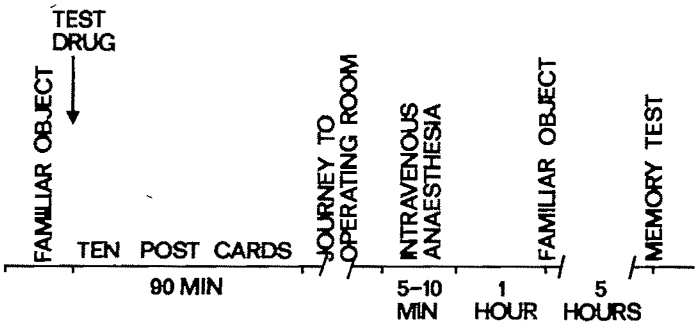

FIG. 2. Plan of the study.

and thereafter a card was shown every 10 min up to a total of 10. The contents of these were emotionally neutral and they were chosen so that no two could be confused readily with each other. The sequence used was the same in all patients.

At each visit the condition of the patient was assessed with regard to the efficacy of the drug as a premedicant, using the method described by Dundee, Moore and Nicholl (1962). A "score" was allotted ranging from 1 (awake, apprehensive and restless) to 5 (lightly asleep) as each card was presented. If the patient was asleep she was roused and asked to identify the card.

After 90 min the patient was brought to the operating theatre, where anaesthesia was induced with 2% methohexitone 1.6 mg kg^{-1} and maintained with 75% nitrous oxide in oxygen, supplemented by additional methohexitone as required.

One hour after recovery from anaesthesia the patient was shown a second familiar object and asked to identify it. Six hours after her operation each patient was visited again. Patients were asked first: "Did I show you anything before you had your tablet?" and second "Did I show you anything after your operation?" Each patient was then asked whether she remembered the journey from the ward to the operating theatre and the i.v. injection.

At the 6-h visit the patient was asked to recall, in any order, as many of the postcards as she could (recall). She was then presented with a sequence of 20 cards in random order, consisting of the 10 seen already and 10 "dummies". (It was explained that some, but not all, of these cards had been seen previously and that the patient had to select those seen previously (recognition).)

Performance on unaided recall and on recognition was scored for each postcard as clear, hazy or nil. Several indices are available by means of which the degree of amnesia might be quantified. In the "control" studies the frequency of complete or partial failure of recognition was very low indeed, occurring in only seven of 400 presentations and this parameter is used in most of the results shown. In addition, the overall frequency of amnesia was calculated as described by Dundee and Pandit (1972). Complete amnesia required failure of recall and recognition, while absence of amnesia indicated complete clarity of recall and recognition. Intermediate grades were classed as partial amnesia. The statistical significance of the findings was calculated on absolute numbers by the χ^2 method with $P<0.05$ as the lower level of significance.

RESULTS

A total of 160 drug observations were made, as well as 40 observations on patients who were given an inert preparation. The groups of patients were broadly comparable with regard to average age and weight (table I).

The frequencies of complete or partial failure of recognition in each group are shown in table II. This gives the percentage frequency of amnesia for the object shown before drug administration

TABLE II. *Percentage frequency of failure of recognition at the times shown following the administration of the various drugs (or combinations). R = memory of object shown before administration of drug (retrograde); J = memory of journey to operating theatre; I = memory of i.v. injection; O = memory of object shown 6 h following administration of drug*

			Time after administration (min)											
Drug	Dose (mg)	R	5	10	20	30	40	50	60	70	80	90	J	I	O
Diazepam	5	0	0	0	0	10	0	0	0	0	10	0	0	0	0
Diazepam	10	5	5	0	0	25	40	25	40	10	15	25	5	0	15
Diazepam	20	0	0	0	10	25	30	25	25	30	50	35	10	0	5
Flunitrazepam	0.5	5	0	5	0	25	30	20	25	15	25	10	5	0	5
Flunitrazepam	1	10	5	5	20	55	50	35	65	30	55	50	5	15	15
Lorazepam	1	0	0	0	0	0	0	0	5	10	10	10	0	0	0
Lorazepam	2	10	0	0	0	0	10	10	20	20	10	30	10	10	70
Lorazepam	4	0	0	0	5	5	25	35	50	45	55	70	65	70	40
Lorazepam + hyoscine	2 1	0	0	0	0	0	10	20	30	30	50	60	20	20	40
Lorazepam + hyoscine	4 1	20	0	0	0	30	20	30	50	50	70	60	80	80	90
Inert	—	2.5	0	0	0	0	2.5	5	0	5	2.5	0	0	0	2.5

(retrograde amnesia), the journey to the operating theatre, the i.v. injection and the object shown 1 h after operation. There was a dose-related amnesic effect for all three benzodiazepines.

Diazepam 5 mg caused no greater impairment of recognition than an inert preparation. A significant amnesic effect occurred with 10 mg and 20 mg beginning 20–30 min after administration and persisting for at least 90 min. The effect of the two larger doses did not differ until 70 min after administration, at which time 20 mg produced a significantly greater frequency of failure of recognition (fig. 3).

Both doses of flunitrazepam caused appreciable failure of recognition beginning at 20–30 min (fig. 4); 1 mg had a significantly greater amnesic effect than 0.5 mg.

The amnesic action of lorazepam was clearly dose-related (fig. 5). The effect of 1 mg did not differ significantly from that of placebo. At all observation times 4 mg produced a significantly greater frequency of failure of recognition than

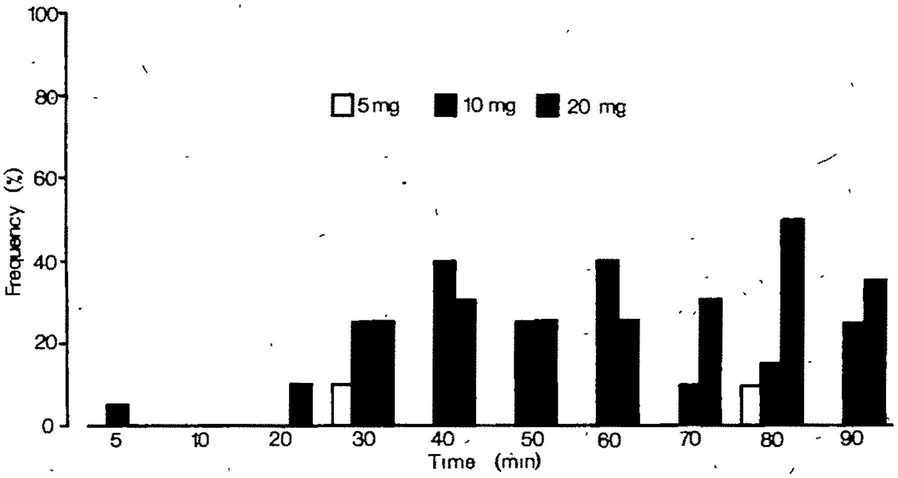

FIG. 3. Percentage frequency of complete or partial failure to recognize the previously seen stimulus at the times shown after the oral administration of diazepam 5 mg, 10 mg and 20 mg.

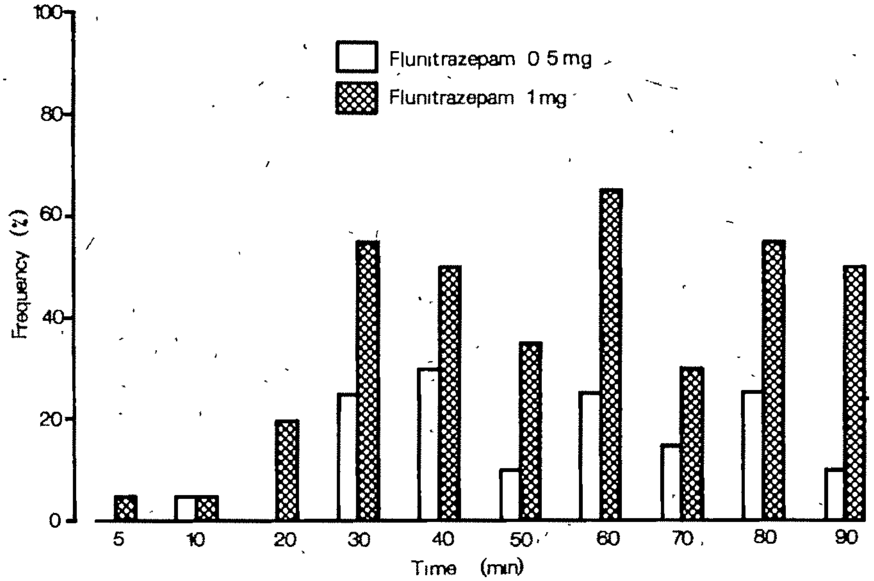

FIG. 4. Percentage frequency of complete or partial failure to recognize the previously seen stimulus at the times shown after the oral administration of flunitrazepam 0.5 and 1 mg.

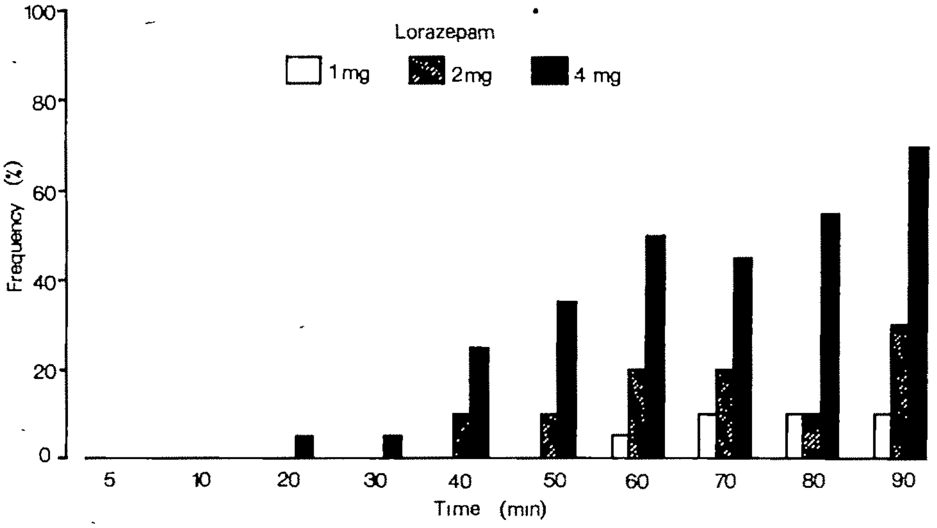

FIG. 5. Percentage frequency of complete or partial failure to recognize the previously seen stimulus at the times shown after the oral administration of lorazepam 1 mg, 2 mg and 4 mg.

2 mg, but even with the greater dose the onset of action did not occur until 40 min after administration.

Flunitrazepam 1 mg and diazepam 20 mg appeared to have a similar potency and time course of action. In contrast lorazepam 4 mg had a more delayed onset of effect and a higher frequency of failure of recognition, and its amnesic effect showed no sign of diminishing at 90 min.

The addition of hyoscine 1 mg to lorazepam 2 mg increased the failure of recognition at 80 and 90 min but this did not occur with the 4-mg dose. Some patients receiving hyoscine complained of dry mouth, dizziness and restlessness, while others who received it in combination with lorazepam 4 mg were more deeply sedated than was considered safe or desirable. The addition of hyoscine did not hasten the onset of amnesia in either case.

The frequency of retrograde amnesia (as measured by failure to remember the object seen before administration of the drug) was negligible in all series (table II). There was also a low frequency of amnesia for the journey to the operating theatre and the i.v. injection, except with lorazepam 4 mg (with or without hyoscine). Persistence of amnesia until 1 h after operation was seen only with lorazepam.

Table III gives the data for failure of recall.

TABLE III. *Percentage frequency of failure of recall at the times shown following the administration of the various drugs (or combinations)*

Drug	Dose (mg)	Time after administration (min)									
		5	10	20	30	40	50	60	70	80	90
Diazepam	5	0	10	0	20	0	10	10	10	10	0
Diazepam	10	10	10	45	50	60	55	85	50	75	40
Diazepam	20	10	5	40	35	50	55	80	65	70	70
Flunitrazepam	0.5	5	15	45	60	50	40	80	50	60	30
Flunitrazepam	1	15	5	60	60	60	45	80	60	75	55
Lorazepam	1	0	5	15	15	0	30	30	30	35	30
Lorazepam	2	0	0	0	0	20	40	50	70	70	80
Lorazepam	4	0	5	15	15	55	55	75	90	75	90
Lorazepam + hyoscine	2 1	10	0	0	10	50	40	80	40	80	90
Lorazepam + hyoscine	4 1	10	10	15	50	50	70	80	70	80	100
Inert	—	12.5	20	17.5	10	10	22.5	12.5	27.5	10	7.5

Clearly there is a difference between failure of recall and recognition, the latter occurring less frequently. The difference between the two frequencies decreased consistently with increasing dosage of all three drugs. Figure 6 expresses this as the difference in the frequency of recall (A) and recognition (B) divided by the frequency of recall.

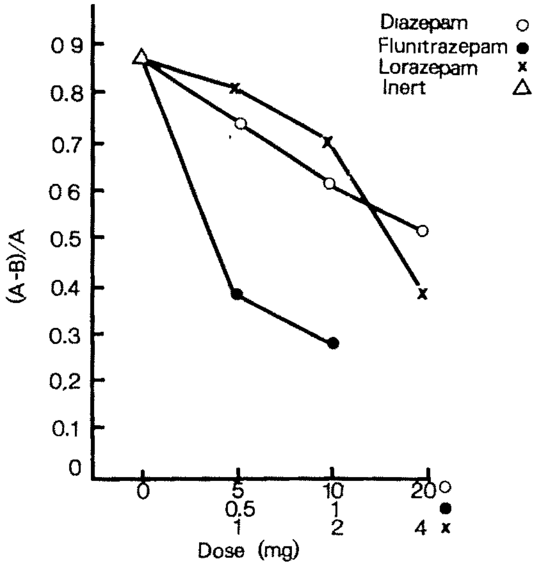

FIG. 6. The relationship between the difference between percentage failure of recall (A) and percentage failure of recognition (B) expressed as a ratio of the former and dose for the three benzodiazepines studied.

Drowsiness and amnesia

Table IV shows the percentage frequency of marked drowsiness or sleep (efficacy score of 4 or 5) for each series. The relationship between this index and failure of recognition with two doses each of diazepam (fig. 7) and lorazepam (fig. 8) is shown clearly; increasing drowsiness and failure of recognition follow a similar time course and are not independent of each other.

With some drugs it was possible to show a relationship between the total number of failures of recognition of postcards and the cumulative "sedation" score in individual patients. Figure 9 is a typical positive finding based on the results with flunitrazepam 1 mg and substantiates the relationship between amnesia and drowsiness with oral benzodiazepines.

Comparison of the oral and i.v. routes

Using published data based on identical methodology from the same centre (Dundee and Pandit, 1972; George and Dundee, 1977) it is possible to compare the effect of diazepam 10 and 20 mg, lorazepam 4 mg and flunitrazepam 1 mg given by the oral and i.v. routes. Table V shows the percentage frequency of any degree of failure of recognition of cards with the same drug given by different routes. Lorazepam 4 mg produced a similar impairment of recognition by both routes, with a more delayed onset of action when taken by mouth. In contrast, the time course of action of both diazepam and flunitrazepam was very different when given by mouth as compared with i.v. administration.

This difference is illustrated in figure 10, which is based on data for diazepam 10 mg and shows that the amnesic effect of the i.v. drug is waning, while that of the oral drug has not yet reached its maximum. This applies also to flunitrazepam.

TABLE IV. *Percentage frequency of marked drowsiness or sleep at the time of the stimulus in various groups*

Drug	Dose (mg)	Time after administration (min)									
		5	10	20	30	40	50	60	70	80	90
Diazepam	10	0	0	15	25	45	40	60	50	50	60
Diazepam	20	0	0	10	25	40	40	55	80	80	80
Flunitrazepam	0.5	0	0	25	40	40	40	65	60	55	45
Flunitrazepam	1	0	0	20	65	60	70	70	70	65	55
Lorazepam	2	0	0	0	40	40	50	50	70	60	70
Lorazepam	4	0	—	0	—	35	—	90	—	—	90
Lorazepam + hyoscine	2 1	0	0	10	10	20	40	50	60	70	90
Lorazepam + hyoscine	4 1	0	0	10	30	60	60	60	70	70	70

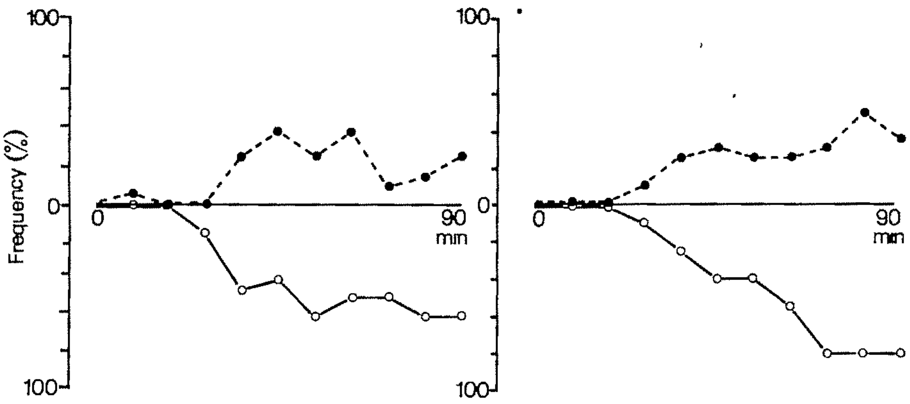

FIG. 7. The relationship between failure of recognition (●—●) and marked drowsiness (○——○) after the oral administration of diazepam 10 mg (left) and 20 mg (right).

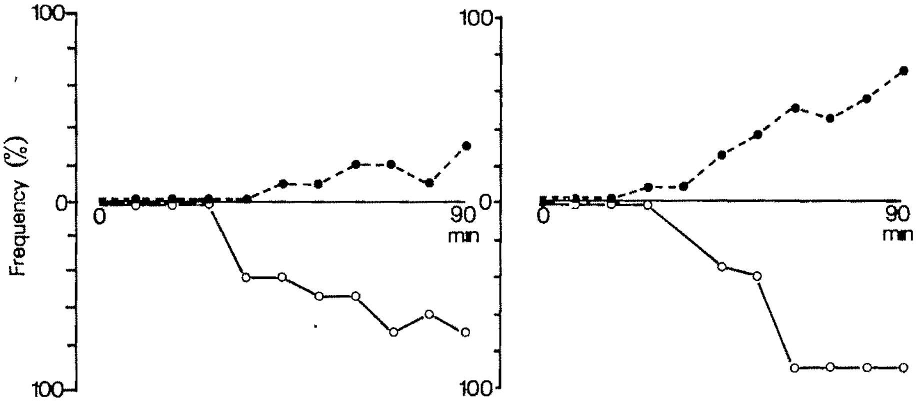

FIG. 8. The relationship between failure of recognition (●—●) and marked drowsiness (○——○) after the oral administration of lorazepam 2 mg (left) and 4 mg (right).

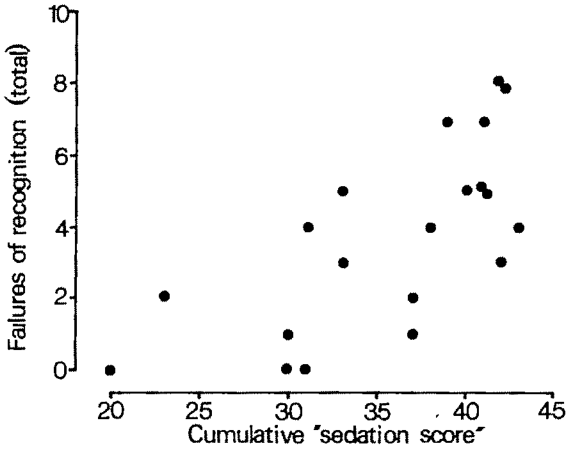

FIG. 9. The relationship between the total number of failures of recognition and the cumulative "sedation score" over 90 min in individual cases after the administration of flunitrazepam 1 mg.

DISCUSSION

The three benzodiazepines, when given orally in doses used normally for premedication, produced dose-related anterograde amnesia. This paralleled closely, both in extent and duration, their soporific action. However, no detectable degree of amnesia was found with minimal tranquillizing doses of diazepam (5 mg) or lorazepam (1 mg).

The ability of premedicant doses of these agents to produce amnesia by the oral route may be a useful adjunct to their anxiolytic and soporific effects. Amnesia for the experimental stimuli (postcards) was much greater than for the emotionally significant experiences of being taken to the operating theatre and being given an i.v. injection. This occurred soon after the 90-min postcard was shown, so that the difference (table II) cannot be

TABLE V. *Percentage frequency of complete and partial failure of recognition with the same drug given by the i.v. and oral routes. (Data on i.v. administration taken from Dundee and Pandit (1972) and George and Dundee (1977))*

Drug	Dose (mg)	Route	Time after administration (min)									
			5	10	20	30	40	50	60	70	80	90
Diazepam	10	i.v.	60	37	17	—	7	—	3	—	—	—
		oral	5	0	0	—	40	—	40	—	—	—
Diazepam	20	i.v.	60	30	30	20	40	40	40	30	20	0
		oral	0	0	10	25	30	25	25	30	50	35
Lorazepam	4	i.v.	15	50	55	70	65	80	60	80	70	75
		oral	0	0	5	5	25	35	50	45	55	70
Flunitrazepam	1	i.v.	65	65	40	—	15	—	10	—	—	—
		oral	5	5	20	—	50	—	65	—	—	—

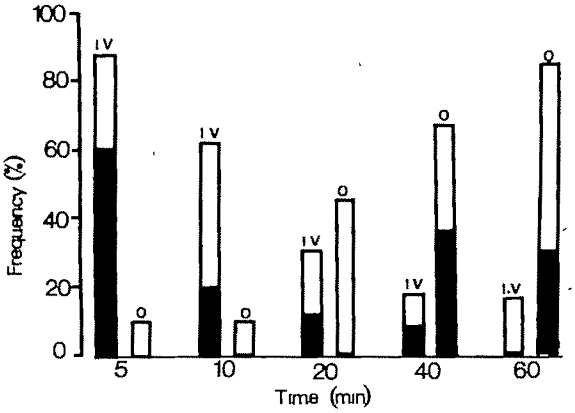

FIG. 10. Percentage frequency of complete (solid) and partial (clear) failure of recognition at the times shown following the i.v. and oral (o) administration of diazepam 10 mg.

explained solely on the basis of time after administration of the drug. It would appear unwise to handle a patient who has had an oral benzodiazepine in any way differently from those having other premedicants on the assumption that they may not remember the events. With lorazepam 4 mg, however, the frequency of amnesia for the journey to the theatre and the injection was similar to that for the postcards and did not differ greatly from that found with the i.v. route.

The difference between lorazepam and the other two drugs with regard to the effect of the emotional significance of the memory stimulus may be a result of the difference in duration of action; the plasma concentrations following 4 mg orally and i.v. are similar 90 min after administration (Dundee et al., 1978), and the frequency of amnesia with oral lorazepam eventually reaches that following i.v. injection. This does not apply to diazepam or flunitrazepam.

To claim a specific amnesic action for a drug it is clearly necessary to demonstrate that the subject was sufficiently awake at and around the time of the stimulus to be able to register it, and to show that subsequent amnesia is not related to a depressed level of consciousness. In several studies using benzodiazepines administered i.v. a method for assessing registration of information was either contained within the experimental design (Clarke et al., 1970; Frumin, Herekar and Jarvik, 1976) or applied clinically (Dundee and Pandit, 1972, Gregg, Ryan and Levin, 1974; George and Dundee, 1977). A striking feature in all of these studies was that amnesia occurred in subjects who appeared conscious and co-operative at the time of the stimulus. No definite correlation between significant drowsiness and amnesia was found by George and Dundee (1977) for i.v. diazepam and flunitrazepam.

In contrast, these two effects were related in the present study when drugs were given orally. Where patients were conscious and co-operative, amnesia was less likely. Thus, the attribution of a specific amnesic action to diazepam and flunitrazepam, which has resulted from the findings in i.v. studies would be difficult to justify from these present studies.

The differences in the time-courses of the amnesic actions of diazepam and flunitrazepam paralleled the plasma concentrations of these two drugs. However, it is not possible to explain the delay in onset of lorazepam on these grounds.

The specific amnesic action after the i.v. but not the oral route of administration of diazepam and flunitrazepam might be a result of the difference in plasma concentrations achieved with the two routes, or perhaps be related to the more rapid increase in plasma concentration following i.v. administration.

Are the amnesic and sedative actions of the drug separate entities, or do they simply reflect progressive steps in cerebral depression? In the case of lorazepam, the only difference between the oral and i.v. routes, as regards amnesia, was the delay in the former attributable to absorption. With both the i.v. (George and Dundee, 1977) and oral routes amnesia correlated closely with drowsiness. The degree of amnesia found with each route was approximately the same after time was allowed for absorption. After oral lorazepam, amnesia occured for emotionally significant as well as for neutral stimuli. While lorazepam amnesia is not separated from sedation, it is of a different and more profound character from that of diazepam or flunitrazepam. For this reason it may be the preferred drug for premedication, particularly on the night before operation.

In this study, retrograde amnesia was a sporadic occurrence which was neither drug- nor dose-related. This is in agreement with previous results (Dundee and Pandit, 1972) which suggested that retrograde amnesia associated with drug action occurred only where sedation had been sufficiently deep to cause some degree of cerebral hypoxia. The administration of diazepam following a strong stimulus would not be expected to suppress the memory of this event; thus it cannot be recommended for this purpose in obstetric anaesthesia (Marshall Barr et al., 1977; Dundee and McKay, 1978). It is important to appreciate that the terms anterograde and retrograde have been confused in the literature (Suri, 1978).

Many studies have shown that hyoscine has an amnesic action, both alone and in combination with diazepam (Hardy and Wakely, 1962; Dundee and Pandit, 1972). Our results suggest that oral hyoscine may slightly increase the amnesic effect of lorazepam, but will not cause a more rapid onset of action. It should not be given with large doses of benzodiazepines.

Our findings agree with those of other workers who concluded that benzodiazepines act upon the early consolidation phase of memory processing, although in a clinical study such as this it was not possible to separate this from an effect on registration.

Both Clarke and colleagues (1970) and Gregg, Ryan and Levin (1974) found that, while impairment of unaided recall by benzodiazepines was, as might be expected, always greater than impairment of recognition, the difference between these two features did not change from control values despite increasing dose. This is interpreted as evidence that benzodiazepine amnesia is not the result of an effect on retrieval of information; this latter type is associated with organic brain disorder and is characterized by an increased difference between recall and recognition performances (Williams and Zangwill, 1952; Victor, 1969); it is interesting that in the present study the difference between impairment of recall and of recognition, taken as a ratio to the former (fig. 6) consistently decreased with increasing dose of each drug, being greatest in the inert group. This is further evidence that benzodiazepine amnesia does not result from an effect on retrieval.

The anaesthetist will be interested in the frequencies of any degree of amnesia with the three benzodiazepines studied, and the findings are summarized in table VI.

TABLE VI. *Percentage frequency of any degree of amnesia at the times shown following various doses of the three benzodiazepines administered orally*

Drug	Dose (mg)	Time after administration (min)									
		5	10	20	30	40	50	60	70	80	90
Diazepam	5	0	10	0	20	0	10	10	10	20	0
	10	10	10	45	55	65	60	85	50	80	55
	20	10	5	40	35	50	60	85	70	75	75
Flunitrazepam	0.5	5	15	45	65	55	40	80	50	65	40
	1	20	10	60	60	75	55	85	60	75	70
Lorazepam	1	0	5	15	15	0	30	35	30	35	35
	2	0	0	0	0	20	40	50	70	70	80
	4	0	5	15	15	55	55	75	90	75	90
Inert	—	12.5	20	17.5	10	10	22.5	12.5	27.5	10	7.5

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EFFET DES BENZODIAZEPINES ORALES SUR LA MEMOIRE

RESUME

On a étudié les effets de l'administration orale de 5, 10 et 20 mg de diazepam, de 0,5 et 1 mg de flunitrazepam et de 1, 2 et 4 mg de lorazepam sur la mémoire de groupes de patients sains avant l'opération. On a pris également du degré de sédation. Toutes les substances ont produit un effet d'amnésie en rapport avec la dose, mais celui-ci n'était pas significatif quand on avait administré 5 mg de diazepam et 1 mg de lorazepam. Des doses plus fortes de diazepam (10 et 20 mg) ont eu pour effet une brève amnésie comparable à celle obtenue au moyen de doses équivalentes de flunitrazepam (0,5 et 1 mg). La même période s'est écoulée jusqu'au début de l'amnésie quand on a administré 4 mg de lorazepam oral ou i.v. et son effet a duré pendant 90 min au moins après administration. Contrairement à l'effet des mêmes substances administrées i.v., la perte de connaissance et la somnolence suivent la même courbe de durée.

DIE WIRKUNG VON MÜNDLICH VERABREICHTEN BENZODIAZEPINEN AUF DAS GEDÄCHTNIS

ZUSAMMENFASSUNG

Die Wirkungen von mündlich verabreichtem Diazepam 5, 10 und 20 mg, Flunitrazepam 0,5 und 1,0 mg und Lorazepam 1, 2 und 4 mg auf das Gedächtnis wurden bei Gruppen von gesunden Patienten vor der Chirurgie studiert. Das Beruhigungsgrad wurde ebenfalls notiert. Eine dosisbezogene amnesische Wirkung wurde in jedem Fall durch die verwendeten Mittel hervorgerufen, obwohl diese Wirkung bei

Diazepam 5 mg und Lorazepam 1 mg unbedeutend war Grössere Dosen von Diazepam (10 und 20 mg) verursachten eine kurzweilige Amnesie, die mit der Wirkung von aquivalenten Dosen von Flunitrazepam (5 mg und 1 mg) vergleichbar war. Bei einer mündlich verabreichten Dosis von Lorazepam 4 mg trat die amnesische Wirkung mit derselben Verzögerung wie bei der intravenösen Verabreichung ein und die Wirkung hielt mindestens 90 Minuten nach der Einnahme an. Im Gegensatz zu der Wirkung derselben Mittel bei intravenöser Verabreichung zeigen Schläfrigkeit und fehlende Wiedererkennung einen ähnlichen Zeitverlauf.

EFECTO DE LAS BENZODIAZEPINAS ORALES SOBRE LA MEMORIA

SUMARIO

Se estudiaron los efectos de la administración oral de 5, 10 y 20 mg de diazepam, de 0,5 y 1 mg de flunitrazepam así como de 1, 2 y 4 mg de lorazepam sobre la memoria de grupos de pacientes sanos antes de la cirujía. Se anotó también el grado de sedación. Todas las substancias produjeron un efecto de amnesia en relación con la dosis, pero éste no fue significante con 5 mg de diazepam ni tampoco con 1 mg de lorazepam. El diazepam en dosis mayores (10 y 20 mg) produjo una amnesia breve comparable con dosis equivalentes de flunitrazepam (0,5 y 1 mg). El plazo transcurrido hasta el inicio de la amnesia después de la administración oral de 4 mg de lorazepam fue análogo al de la administración i.v. y sus efectos se prolongaron durante 90 min por lo menos después de la administración. En contraste con los efectos de las mismas substancias administradas por vía i.v., la falta de conocimiento y modorra siguen una curva de tiempo similar.

Br. J. Anaesth. (1980), 52, 1259

LORAZEPAM AND MORPHINE FOR I.V. SURGICAL PREMEDICATION

J. L'ARMAND, L. A. VREDEVOE, J. T. CONNER, G. P. HERR AND D. SCHEHL

SUMMARY

The effects of i.v. lorazepam alone, in doses of 2 mg and 4 mg, and combined with morphine 5 mg, were studied. Sedation, relief of anxiety, lack of recall, patient acceptance, physician acceptance and side-effects were evaluated. The addition of morphine to lorazepam significantly improved sedation and relief of anxiety. Physician acceptance and patient acceptance showed no significant difference between any of the combinations. Lack of recall was enhanced by increasing the dose of lorazepam from 2 mg to 4 mg, independent of the addition of morphine. The only significant side-effect was restlessness which occurred in 15% of patients receiving lorazepam 4 mg and 3% of patients receiving lorazepam 2 mg, again independent of the addition of morphine.

The introduction of lorazepam has created interest in its use for premedication. The effects of lorazepam alone (Conner et al., 1976, 1978) and its combination with atropine and hyoscine (Conner et al., 1978) have been reported. The present investigation concerns the use of i.v. lorazepam alone (2 mg or 4 mg), and in combination with i.v. morphine 5 mg. Relief of anxiety, sedation, lack of recall, acceptance by both the patient and physician and side-effects are evaluated.

METHODS

One hundred and twenty patients in the age range 18–76 yr undergoing a variety of surgical operations were assigned randomly to four groups, each group receiving different preoperative medication: i.v. lorazepam 2 mg, lorazepam 4 mg, lorazepam 2 mg combined with morphine 5 mg, and lorazepam 4 mg combined with morphine 5 mg.

The drugs were administered over a period of 1 min approximately 1 h before surgery, using a double-blind technique. All observations were made by a trained nurse observer.

Before premedication, each patient was asked to evaluate his level of anxiety as negligible, mild, moderate or severe. Four minutes after medication, his sedation relative to his unmedicated state was rated by the nurse observer as 0 (unchanged), 1+, 2+, 3+, 4+ (improved), or 1−, 2−, 3−, 4−, (worse). The patient was asked to rate his level of anxiety using a similar scale, and was asked if the overall sensation of the drug was pleasant, unpleasant, or neutral. The evaluations were repeated at 8, 16 and 32 min.

Recall was tested by showing the patient a randomized series of pictures of familiar objects or scenes 1, 2, 4, 8, 16 and 32 min after injection of the drug. After 24 h the patient was asked to pick out the pictures previously shown to him from an array of eight pictures. Recall of pre-medication, the operating room and the recovery room were also sought.

At 24 h the patient was asked to rate the premedication as poor (0), fair (1+), good (2+), or excellent (3+). Each patient was asked if he would like to receive the drug again for future surgery.

Just before induction of anaesthesia, the anaesthetists were asked to rate the premedicant as poor (0), fair (1+), good (2+), or excellent (3+). They were also asked if they would use the drug again.

Statistical analysis was performed by transforming the raw scores to ridits and using the analysis of variance procedure (Selvin, 1977).

The raw scores were transformed into ridits using the combined lorazepam 4-min scores from this and previous studies (Conner et al., 1976, 1978; Pagano et al., 1978) as the reference population. We tested for an overall drug and dose response using repeated measures of analysis of variance with an appropriate test for time trends. Significance was taken at $P \leqslant 0.05$.

RESULTS

Anxiety

The changes in anxiety as scored by the patient are shown in table I. The addition of morphine

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0007-0912/80/121259-05 $01.00

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TABLE I. *Patient anxiety relief scored by patient (0±4 scale)*

	Lorazepam 2 mg	Lorazepam 4 mg	Lorazepam 2 mg + morphine 5 mg	Lorazepam 4 mg + morphine 5 mg
Mean scores				
4 min	1.31	1.83	1.68	2.04
8 min	1.71	2.34	2.18	2.54
16 min	2.02	2.75	2.47	3.15
32 min	2.56	3.11	2.87	3.35
Ridit scores				
4 min	0.414	0.561	0.518	0.609
8 min	0.521	0.673	0.631	0.713
16 min	0.588	0.766	0.702	0.846
32 min	0.702	0.824	0.756	0.856

5 mg produced a significant decrease in patient anxiety, with lorazepam 4 mg scoring significantly better than lorazepam 2 mg.

When the individual time periods were analysed separately, significant differences were detected at 4, 8, and 16 min only. The most significant improvement was seen with lorazepam 4 mg plus morphine 5 mg compared with lorazepam 2 mg.

Sedation (table II)

Sedation as evaluated by the nurse observer also showed significant improvement by the addition of morphine 5 mg to either lorazepam 2 mg or 4 mg. However, the most significant improvement ($P < 0.01$) occurred with the increased dose of lorazepam (2 mg to 4 mg).

Again, the significant differences were limited to the periods 4, 8, and 16 min.

Patient acceptance and physician acceptance (tables III, IV)

There was no significant difference between the four drug combinations in patient acceptance or physician acceptance.

Recall (table V)

Failure of recall was significantly greater during the period before operation with lorazepam 4 mg than with lorezapam 2 mg, with or without morphine. In the recovery room, the differences between the four combinations were slight, although the greater dose of lorazepam produced somewhat less recall.

Side-effects

Side-effects were not frequent and were not bothersome to the patient. The one possible exception to this was restlessness which appeared to be related to the dose of lorazepam. Restlessness occurred approximately 15–30 min after injection and was seen in 15% of patients receiving lorazepam 4 mg alone or with morphine, and in 3% of patients receiving lorazepam 2 mg alone or with morphine. The addition of morphine did not

TABLE II. *Patient sedation scored by nurse observer (0±4 scale)*

	Lorazepam 2 mg	Lorazepam 4 mg	Lorazepam 2 mg + morphine 5 mg	Lorazepam 4 mg + morphine 5 mg
Mean scores				
4 min	0.45	1.28	1.15	1.47
8 min	0.92	1.66	1.79	2.32
16 min	1.50	2.41	2.36	2.81
32 min	2.39	2.55	2.59	3.35
Ridit scores				
4 min	0.291	0.504	0.486	0.574
8 min	0.412	0.585	0.631	0.740
16 min	0.535	0.726	0.736	0.809
32 min	0.687	0.724	0.732	0.875

TABLE III. *Patient acceptance (0–3) at 24 h and patient's subjective rating at 4 min*

	Lorazepam 2 mg	Lorazepam 4 mg	Lorazepam 2 mg + morphine 5 mg	Lorazepam 4 mg + morphine 5 mg
Acceptance (percentage of patients)				
Poor	0%	0%	3%	3%
Fair	0%	3%	3%	3%
Good	44%	40%	33%	15%
Excellent	56%	57%	61%	79%
Mean score	2.55	2.53	2.53	2.71
Ridit score	0.502	0.500	0.520	0.599
Subjective rating (percentage of patients)				
Pleasant	58%	63%	70%	56%
Unpleasant	0%	0%	3%	3%
No opinion	42%	37%	27%	41%
Percentage of patients who would take drugs again	93%	97%	97%	97%

TABLE IV. *Physician's acceptance (0–3) at time of surgery*

	Lorazepam 2 mg	Lorazepam 4 mg	Lorazepam 2 mg + morphine 5 mg	Lorazepam 4 mg + morphine 5 mg
Percentage of patients				
Poor	15%	23%	0%	22%
Fair	30%	27%	35%	12%
Good	55%	40%	45%	50%
Excellent	0%	10%	20%	16%
Physician's acceptance				
Mean score	1.41	1.37	1.84	2.59
Ridit score	0.507	0.476	0.615	0.542
Percentage of physicians who will use the drug again	75%	75%	92%	77%

TABLE V. *Failure to recall (values in percent)*

	Lorazepam 2 mg	Lorazepam 4 mg	Lorazepam 2 mg + morphine 5 mg	Lorazepam 4 mg + morphine 5 mg
Memory card				
1 min	7	10	6	15
2 min	7	29	19	29
4 min	13	29	19	27
8 min	20	52	22	56
16 min	25	45	33	58
32 min	45	64	39	61
Operating room	40	74	27	79
Recovery room	73	84	77	84

appear to change the frequency of this side-effect. Restlessness was not marked in most patients.

DISCUSSION

A number of studies have been published describing lorazepam as an effective premedicant (Blitt, 1976; Conner et al., 1976, 1978; Pandit, Heisterkamp and Cohen, 1976; Dundee et al., 1977). Lorazepam is not known to have analgesic properties. This study was designed to assess its effects when combined with morphine.

In an earlier study, it was reported that lorazepam combined with hyoscine produced agitation and restlessness which prohibited their use together (Pagano et al., 1978). There was concern about possible drug interaction seen with lorazepam.

In this study the frequency of restlessness seen with lorazepam alone was dose related (3% with lorazepam 2 mg and 15% with lorazepam 4 mg). The addition of morphine did not change the frequency of this side-effect. This frequency of restlessness, or agitation, seen with lorazepam alone is greater than has been previously reported (Connor et al., 1978; Pagano et al., 1978). In these earlier studies, patients were not closely observed after 30 min. However, it was suspected that restlessness might occur later and this was specifically sought in this study. Indeed it was found that many patients did display restlessness at these later times.

The combination of morphine with lorazepam did not produce any troublesome side-effects specifically related to drug interactions. In fact, lorazepam appeared to diminish unpleasant side-effects seen with i.v. morphine in previous studies (such as tingling, heaviness, flushing and nausea). The addition of morphine to lorazepam enhanced sedation and relief of anxiety, although patient acceptance, physician acceptance and lack of recall were not significantly altered. It is important to note that patient acceptance scores of lorazepam alone are very high, thus making improvement difficult.

Likewise, physician acceptance scores for the study drugs are high in comparison to our other studies. This is despite a tendency by physicians to rate the effects of premedicants lower than do patients. It is again difficult to demonstrate significant difference in physician acceptance. Although high, sedation and anxiety relief scores of lorazepam are equalled by other drugs studied, and can be improved. Morphine has never been known to produce lack of recall and, as such, no change in recall was expected.

The addition of morphine to lorazepam proved to be a compatible combination of drugs for surgical premedication. There were no adverse effects from the combination and, in general, the drugs complemented each other.

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LORAZEPAM ET MORPHINE DANS LA PREMEDICATION I.V. EN CHIRURGIE

RESUME

On procéda à l'étude des effets du lorazepam seul en doses de 2 mg et 4 mg, ainsi que combiné avec 5 mg de morphine. Des évaluations de la sédation, du soulagement de l'angoisse, de la perte de mémoire, de l'acceptation par le patient, de l'acceptation du médecin et des effets secondaires ont été réalisées. L'addition de morphine au lorazepam améliora grandement la sédation et le soulagement de l'angoisse. L'acceptation tant du médecin que du patient ne fit état d'aucune différence significative entre l'une quelconque des combinaisons. La perte de mémoire fut plus forte lorsqu'on augmentait la dose de lorazepam de 2 à 4 mg, indépendamment de l'addition de morphine. Le seul effet secondaire significatif fut l'agitation dont firent preuve 15% des patients auxquels on avait administré 4 mg de lorazepam et 3% de ceux auquels on avait administré 2 mg de lorazepam, une fois encore indépendamment de l'addition de morphine.

LORAZEPAM UND MORPHIN BEI DER INTRAVENÖSEN CHIRURGISCHEN VORBEHANDLUNG

ZUSAMMENFASSUNG

Die Wirkung von intravenös verabreichtem Lorazepam allein, in Dosen von 2 mg und 4 mg, und mit Morphin 5 mg kombiniert wurden untersucht. Beruhigungseffekt, Erleichterung

des Angstzustandes, nachlassendes Erinnerungsvermögen, Verträglichkeit beim Patienten, günstige Aufnahme bein Arzt und Seiteneffekte wurden ausgewertet. Durch Beimischung von Morphin wurde der Beruhigungseffekt und die Erleichterung von Angstzuständen bedeutend verbessert. In Bezug auf Verträglichkeit und Aufnahme bei dem Arzt waren zwischen den einzelnen Kombinationen keine bedeutende Unterschiede festzustellen. Das Nachlassen des Erinnerungsvermogens wurde durch eine Vergrösserung des Lorazepamanteils von 2 mg auf 4 mg gesteigert, unabhängig von der Beimischung von Morphin. Der einzige bedeutende Seiteneffekt war eine Ruhelosigkeit, die sich bei 15% der Patienten einstellte, die Lorazepam 4 mg bekommen hatten und bei 3% von denen, die Lorazepam 2 mg bekommen hatten, wiederum unabhängig von der Beimischung von Morphin.

LORAZEPAM Y MORFINA EN LA PREMEDICACION QUIRUGICA INTRAVENOSA

SUMARIO

Se estudiaron los efectos de la administración de 2 mg y de 4 mg de lorazepam sóla por vía intravenosa, y en combinación con 5 mg de morfina. Se evaluaron la sedación, eliminación de la ansiedad, la falta de memoria, la aceptación que presentó el paciente y la aceptación del médico por parte de aquel, además de los efectos secundarios. La incorporación de morfina al lorazepam mejoró significativamente la sedación y la eliminación de la ansiedad. La aceptación del paciente y del médico no mostraron diferencia significativa alguna entre las dos combinaciones. El fallo de la memoria se puso de manifiesto al incrementar la dosis de lorazepam desde 2 mg a 4 mg, independientemente de la presencia o ausencia de morfina. El único efecto secundario significativo fue la inquietud que tuvo lugar en un 15% de los pacientes que recibieron 4 mg de lorazepam y en un 3% de los pacientes que recibieron 2 mg de lorazepam, independientemente de la presencia o ausencia de morfina.

Br. J. Anaesth. (1980), 52, 1265

POSTOPERATIVE EFFECTS OF METHYLPHENIDATE

M. E. DODSON AND J. M. FRYER

SUMMARY

A double-blind study is described in which the analgesic and analeptic properties of methylphenidate were investigated in 63 patients following surgery. No effect of methylphenidate on postoperative pain was observed. However, methylphenidate reduced sedation up to 30 min after operation, and improved respiratory function up to 180 min in patients receiving halothane. No conclusive evidence of improvement in mood was obtained, and occasional undesirable behavioural effects of methylphenidate were seen.

Methylphenidate, an analeptic agent with a potency mid-way between those of caffeine and the amphetamines (Meier, Gross and Tripod, 1954), has central nervous system, cardiac and respiratory stimulant activity. It has been used to decrease waking time after general anaesthesia (Christensen, 1958; Gale, 1958) and to reverse coma resulting from drugs or minor degrees of brain injury (Hoagland, 1965). Brichard and Johnstone (1970) described its use in the prevention of the shivering associated with halothane anaesthesia and Johnstone (1974), reporting on its analgesic properties, suggested its use for the relief of pain after operation.

Since any drug which combines analeptic with analgesic properties could be useful in the postoperative period, a double-blind trial was carried out to assess further the analgesic and other effects of methylphenidate when administered i.v. at the end of anaesthesia.

PATIENTS AND METHODS

The subjects were females aged 16–70 yr, weighing 45–90 kg and undergoing intra-abdominal gynaecological procedures. All were fit (ASA I or II). Patients were excluded if they were receiving regular medication with analgesics, major tranquillizers or antidepressants, or if they had a history of psychiatric illness. Pregnant patients were excluded, as were those who had been given a halothane anaesthetic within the preceding 6 weeks. At the preoperative visit, consent was obtained and the patient weighed.

Vital capacity (VC) and forced expiratory volume in one second (FEV_1) were determined using a Vitalograph and peak flow measurements were obtained using a Wright's peak flow meter. Pain, mood and anxiety were measured using linear analog scales (Kellner, Kelly and Sheffield, 1968; Zealley and Aitken, 1969; Huskisson, 1974).

Promethazine 50 mg was given by mouth 2–3 h before operation to all except two patients, who were given oral lorazepam 2.5 mg. All patients were anaesthetized with thiopentone and nitrous oxide. Alcuronium was administered to produce neuromuscular blockade, which was antagonized with neostigmine and atropine. The first 38 patients received also halothane 0.5–1.0% for maintenance of anaesthesia. The other 25 patients received fentanyl 1.5 or 3 μg/kg body weight instead of halothane, the smaller doses of fentanyl being given to patients having tubal ligation.

Patients were allocated randomly to receive either methylphenidate or placebo using numbered envelopes. An assistant opened the next envelope in the series and followed the instructions to prepare either 2 ml of sterile water, or methylphenidate 40 mg in 2 ml of sterile water (the preparation). The syringe was identified with the number on the envelope and given to the anaesthetist. Approximately 10 min before the end of the operation, halothane was discontinued and the preparation 0.2 ml per 10 kg body weight was injected. The dose of methylphenidate was thus 0.4 mg/kg body weight.

The e.c.g. was recorded before and for up to 10 min after the administration of the preparation, and the heart rate derived from the record. Systolic arterial pressure was recorded before giving the preparation, 5 min later and at 5 min-intervals

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0007–0912/80/121265–06 $01.00

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until neostigmine and atropine were given. At extubation, salivation was assessed as minimal or much (Dodson and Eastley, 1978).

After operation, the time from extubation to the time of first response to command was noted. The patients were observed for shivering and for behaviour suggesting stimulation of the central nervous system or elevation of mood. Measurements of heart rate and arterial pressure were carried out routinely by the nursing staff.

Thirty and 180 min after operation, sedation was assessed as no sedation (0) increasing degrees of sedation (1 and 2) or very deeply asleep (3) (Dodson, Hussain and Matheson, 1978). Respiratory function tests and linear analog scores were repeated at these times, and on the 1st and 2nd days after operation. A note was made of all drugs given to the patients during the first 24 h after operation, and the patients were asked about the quality of sleep during their first night following operation.

All results were analysed statistically using Students t test or Chi-squared test. Significances are given as $P<0.05$, $P<0.01$, or $P<0.001$.

RESULTS

A total of 63 patients was studied. The distribution of these patients between the two techniques of anaesthesia and methylphenidate or placebo is shown in table I. The age and weight distributions for the four groups were similar.

TABLE I. *Number and type of operations for each anaesthetic. HP = halothane–placebo; HM = halothane–methylphenidate; FP = fentanyl–placebo; FM = fentanyl–methylphenidate*

	HP	HM	FP	FM
Hysterectomy	9	9	5	5
Laparotomy	7	5	7	3
Tubal ligation	3	5	1	4
Total	19	19	13	12

Some measurements were not made in all patients. Therefore in each table in which the number of values used for analysis differs from the number of patients in that group, the number of values is given in parenthesis.

Respiratory function

There was a highly significant deterioration ($P<0.001$) in respiratory function at 30 and 180 min after operation in all groups (table II), and a less significant deterioration on the 1st and 2nd days after operation. The greatest deterioration was seen in the halothane–placebo (HP) group at 30 and 180 min and there was significantly less deterioration when methylphenidate was given with the halothane. In the fentanyl–methylphenidate (FM) group, there was less deterioration in respiratory function compared with the fentanyl–placebo (FP) group, but this difference was not significant. The changes on the 1st and 2nd days after operation were similar for the four groups.

Cardiovascular system

There was a highly significant increase in heart rate 5 min and 10 min after methylphenidate compared with placebo for both techniques of anaesthesia (table III). Systolic arterial pressure was greater also, but the difference was only significant at 5 min for the halothane–methylphenidate (HM) group compared with HP. Fewer readings were obtained at 10 min because anaesthesia had been discontinued in some patients. These increases in heart rate and arterial pressure were not seen 30 min after operation.

Examination of the e.c.g. showed occasional ectopic beats in a few patients in each group. Only one dysrhythmia was seen—pulsus bigeminus in a patient who received halothane and methylphenidate, and whose perineum had been infiltrated with adrenaline. Normal rhythm was restored when neostigmine and atropine were given.

Pain

The linear analog scores are shown in table IV. There was no significant difference in pain scores at 30 and 180 min when the patients receiving methylphenidate were compared with those receiving placebo. The only significant difference was seen when patients receiving placebo were compared for the two anaesthetics. The FP group had a significantly lower pain score 30 min after operation than did the HP group.

Comparing the times from end of operation to the first dose of analgesic, there was no difference between the methylphenidate and placebo groups. However, when the halothane groups were compared with the fentanyl groups, the latter did not require analgesia until significantly later than the halothane patients (table V).

TABLE II. *Mean changes (±SEM) in respiratory measurements from preoperative values at 30 min and 180 min after operation. Comparison of HP and HM;* *P<0.05; **P<0.01

	HP		HM		FP		FM	
	30 min (16)	180 min (16)	30 min (16)	180 min (16)	30 min (11)	180 min (12)	30 min (12)	180 min (12)
VC (litre)	−2.08**	−1.83*	−1.49**	−1.33*	−1.67	−1.53	−1.46	−1.38
SEM	0.16	0.15	0.13	0.16	0.26	0.21	0.20	0.12
FEV$_1$ (litre)	−1.73*	−1.5*	−1.22*	−1.12*	−1.54	−1.35	−1.15	−1.19
SEM	0.16	0.13	0.11	0.13	0.23	0.27	0.17	0.14
Peak flow (litre)	−243	−198	−206	−186	−214	−206	−228	−205
SEM	12.5	16.4	20.3	20.3	21.1	21.1	16.2	15.0

TABLE III. *Mean changes (±SEM) in heart rate and arterial pressure 5 and 10 min after the administration of the preparation. Comparison of HP and HM* ***P<0.001; *P<0.05. *Comparison of FP and FM·* ***P<0.001

	HP		HM		FP		FM	
	5 min	10 min	5 min	10 min	5 min	10 min	5 min	10 min
Heart rate	−5.8***	−4.5***	+22***	+14.5***	−2.2***	−4.7***	+17.7***	+21.3***
(beat min^{-1})		(10)		(11)		(12)		(9)
SEM	1.6	2.7	2.0	2.8	1.6	2.0	3.0	3.7
Arterial pressure	+1.05*	+1.17	+2.14*	+1.62	−0.16	−0.2	+0.94	−0.19
(kPa)		(13)		(16)		(12)		(7)
SEM	0.25	0.32	0.42	0.59	0.23	0.28	0.67	1.22

TABLE IV. *Postoperative pain mean linear analog scores (mm±SEM). Comparison of HP and FP:* **P<0.01

	HP		HM		FP		FM	
	30 min	180 min	30 min	180 min	30 min	180 min	30 min	180 min
Mean	69.4**(16)	65.9 (16)	57.7 (17)	70.8 (18)	49.4**(11)	60.2 (12)	59.1 (12)	69.1 (12)
SEM	4.3	5.6	6.1	6.3	4.4	4.2	6.1	6.9

TABLE V. *Time (min±SEM) from end of operation to receiving first dose of analgesic. Comparison of HP and FP:***P<0.01

	HP	HM	FP	FM
Mean	50.7**	57.7	132**	109
SEM	12.9	14.7	23.6	33.2

Mood

The patients were all more miserable after operation than before as shown by the increase in mood score (table VI). This change was significant only for the HP patients. The deterioration in mood was less in the patients who received methylphenidate, but the difference compared with placebo was not significant.

Anxiety

This was less in all patients 30 min after operation, but no change was significant.

Sedation

In the halothane group, methylphenidate shortened the time to first response to command from a mean of 6 min±SEM 1.0 in the HP group to 3.6 min±SEM 0.8 in the HM group ($P<0.05$). All the fentanyl patients were awake within 4 min of the end of operation.

The degree of sedation at 30 and 180 min after operation was analysed by dividing the patients into awake (0) and sedated (1, 2 and 3). It can be seen (table VII) that sedation at 30 min was significantly less in both groups of patients who

TABLE VI. *Mean changes after operation in mood linear analog scores (mm ± SEM) from values before operation. Significant change from preoperative score:* *$P < 0.05$; **$P < 0.01$

	HP		HM		FP		FM	
	30 min	180 min	30 min	180 min	30 min	180 min	30 min	180 min
Mean	+16.6**(16)	+14* (16)	+7.5 (17)	+7.6 (18)	+14.2 (11)	+11.3 (12)	+8.7 (12)	+12.9 (12)
SEM	4.4	5.5	5.5	3.7	6.6	5.7	6.8	7.2

TABLE VII. *Sedation 30 min and 180 min after operation*

	HP		HM		FP		FM	
	Awake	Asleep	Awake	Asleep	Awake	Asleep	Awake	Asleep
30 min	1	18	15	4	5	8	12	0
	Significant difference ($P < 0.001$)				Significant difference ($P < 0.01$)			
180 min	15	4	16	3	9	4	11	1
	n.s.				n.s.			

TABLE VIII. *Behaviour after operation*

	HP	HM	FP	FM
Talkative	1	1	—	3
Crying and restless	—	2	—	2
Euphoric	—	—	—	1
Shivering	4	—	—	—
Catatonia	—	1	—	—
Head rolling	3	—	—	—

were given methylphenidate when compared with the corresponding placebo group.

Behaviour effects

These are listed in table VIII. The catatonic episode lasted 40 min and during this time it was impossible to communicate with the patient, though she responded non-purposefully to painful stimuli.

Salivation

There was significantly less salivation in the HM group compared with HP ($P < 0.05$), but this difference was not seen in the patients who had received fentanyl.

DISCUSSION

This study was designed initially to investigate the analgesic properties of methylphenidate. Therefore, in the first part of the study, no analgesic drugs were used for premedication or during anaesthesia. When it became apparent that methylphenidate did not improve analgesia after operation in these circumstances, fentanyl was used instead of halothane, but again, no beneficial effect of methylphenidate on postoperative pain could be demonstrated. These findings contrast with those of Johnstone (1974). His anaesthetic technique differed from the two techniques used in this study in that pethidine 50 mg and droperidol 10 mg were given for premedication, and propanidid was used to induce anaesthesia. Also he used larger doses of methylphenidate, that is 40–80 mg, compared with the 18–36 mg (mean 26 mg) used in this study. These differences could account for the presence of analgesia apparently caused by methlyphenidate in his patients.

Elevation of mood and relief of anxiety could be beneficial to patients after operation. Linear analog scores were used to measure both anxiety and mood since their use is established and since patients would be unable to carry out more complex tests such as those involving word selection (Wassenaar et al., 1973) in the period soon after operation.

There was no evidence of any effect of methylphenidate on anxiety, but there was some evidence from the mood scores that patients were less miserable after methylphenidate. However, in all groups, mood was more depressed after operation than before, a change that was significant for the HP group at 30 min and 180 min after operation.

Elevation of mood after methylphenidate was also evident in the four patients who were talkative and the one who was euphoric. However, stimulation of the central nervous system caused restlessness and crying in four patients, a feature not seen in patients who had received the placebo. Similar behaviour after methylphenidate has been described by Gale (1958) and Roberts (1961), but both authors report similar behaviour in patients who were not given methylphenidate. In fact in Gale's study, the frequency of coughing, crying and excitement was slightly less in the methylphenidate group.

A strange effect of methylphenidate was the catatonia. One author (M.E.D.) has seen a similar episode which lasted 4 h in a patient given methylphenidate 20 mg after operation. Bortoluzzi and colleagues (1963) mention "muteness" as a side-effect of methylphenidate.

A shortening of recovery time after anaesthesia has been reported by Gale (1958) with methylphenidate. In this study, a shortening of recovery time was observed only after halothane, as the patients recovered quickly after fentanyl with or without methylphenidate. This study demonstrated also a decrease in sedation 30 min after operation in both groups given methylphenidate. This decrease was not seen 180 min after operation, but by that time, 80% of the patients had been given a dose of narcotic analgesic. Animal experiments have demonstrated that the increased activity caused by methylphenidate is followed often by a state of decreased activity, or even of exhaustion (Meier, Gross and Tripod, 1954). This is obviously a possibility in the human, but no reports of studies of this aspect of recovery from anaesthesia could be found.

An increase in respiratory frequency has been observed after methylphenidate in both animals and man (Meier, Gross and Tripod, 1954; Roberts, 1961; Martin et al., 1971). This study demonstrated that the deterioration in VC and FEV_1, which occurred after operation in all groups, was less in the patients who were given methylphenidate. However, the difference compared with placebo was only significant after halothane and was present still 180 min after operation despite the fact that, by this time, 14 of the 16 patients had received a narcotic analgesic.

Increases in heart rate and arterial pressure have been reported after methylphenidate. In this study, the increase in heart rate was of a greater degree of significance than the increase in arterial pressure. Gale (1958), Roberts (1961) and Martin and co-workers (1971) reported only a moderate increase in arterial pressure, but did not measure heart rate. Bortoluzzi and colleagues (1963) reported heart rate changes similar to those described here. The lack of a marked increase in arterial pressure is probably associated with the α-blocking effect of methylphenidate described by Johnstone (1974).

There are no reports of arrhythmia after methylphenidate. The one arrhythmia in this series occurred in a patient who had been given three drugs which have an effect on heart rate. The restoration to normal rhythm by neostigmine confirms the observations of Brichard and Johnstone (1970).

Roberts (1961) noted constant head movements in some patients after methylphenidate, and this seems to be a common occurrence in some animals (Meir, Gross and Tripod, 1954). In this study, the only patients in whom head rolling was observed had not been given methylphenidate. Another reported side-effect of methylphenidate is vomiting (Gale, 1958; Bortoluzzi et al., 1963). This study did not demonstrate any increase in emergence vomiting, possibly because of the moderate dose of methylphenidate used.

Shivering occurred in four patients of the 19 in the HP group, but none of the HM group, confirming the observations of Bortoluzzi and colleagues (1963). Methylphenidate may be of value when it is important to have increased wakefulness and respiratory stimulation in the early period after operation. These effects were most significant after the halothane anaesthetic. An added advantage of using methylphenidate after halothane is the prevention of shivering. However, its use may be accompanied by crying and restlessness, and catatonia may be seen occasionally. It is possible that the use of larger doses of analgesic drugs, or of tranquillizers, could prevent the adverse effects of methylphenidate while leaving intact its beneficial effects on respiration and shivering.

ACKNOWLEDGEMENTS

We would like to thank Professor V. R. Tindall for permission to study his patients.

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CONSEQUENCES POSTOPERATOIRES DU METHYLPHENIDATE

RESUME

On décrit une étude double aveugle au cours de laquelle des recherches ont été effectuées en ce qui concerne les propriétés analgésiques et analeptiques du méthylphénidate administré à 63 malades à la suite d'opérations chirurgicales. Le méthylphénidate n'a pas eu d'effet notable sur les douleurs postopératoires. Toutefois, il a permis de réduire la sédation à 30 min après l'opération et d'améliorer la fonction respiratoire jusqu'à 180 min chez des patients auxquels on avait administré de l'halothane. Aucune preuve d'amélioration de l'humeur ne s'est manifestée et le méthylphénidate a eu des conséquences inopportunes éventuelles sur le comportement.

POSTOPERATIVE AUSWIRKUNGEN VON METHYLPHENIDAT

ZUSAMMENFASSUNG

Es wird eine Doppelblindstudies beschrieben, bei der die schmerzlindernden und analeptischen Eigenschaften von Methylphenidat bei 63 Patienten nach der Chirurgie untersucht wurden. Dabei wurde keine Einwirkung des Methylphenidats auf postoperative Schmerzen festgestellt. Bis zu 30 Minuten nach der Operation reduzierte Methylphenidat jedoch den Beruhigungseffekt und bis zu 180 Minuten nach der Operation verbesserte es die Atmungsfunktion bei Patienten, die Halothan bekommen hatten. Es wurden keine überzeugende Beweise fur eine Stimmungserhebung gefunden und es wurden gelegentlich unerwünschte Verhaltungsauswirkungen beobachtet.

EFECTOS POSTOPERATORIOS DEL METILFENIDATO

SUMARIO

Se describe un estudio doble-ciego durante el cual se averiguó las propiedades analgésicas y analépticas del metilfenidato administrado a 63 pacientes después de operaciones quirúrgicas. No se observó ningún efecto del metilfenidato sobre el dolor postoperatorio. Sin embargo, el metilfenidato tuvo por efecto reducir la sedación hasta 30 min después de la operación, y mejorar la función respiratoria hasta 180 min en pacientes a quienes se había administrado halotano. No se obtuvo ninguna prueba conclusiva de mejoramiento del humor y se observaron efectos indeseables fortuitos de comportamiento debidos al metilfenidato.

Br. J. Anaesth. (1980), 52, 1271

RESPIRATORY FUNCTION DURING CERVICAL AND THORACIC EXTRADURAL ANALGESIA IN PATIENTS WITH NORMAL LUNGS

M. TAKASAKI AND T. TAKAHASHI

SUMMARY

Lung volumes, expired gas volumes, tests of ventilatory capacity and blood-gas tensions were measured in women before and after induction of cervical or thoracic extradural analgesia using 2% mepivacaine. Inspiratory capacity, vital capacity, total lung capacity and FEV_1 all decreased significantly 30 min after both cervical and thoracic extradural blocks. The changes observed during cervical block were significantly greater than those observed during thoracic extradural analgesia. Expiratory reserve volume and functional residual capacity decreased significantly after thoracic extradural block, but did not change after cervical extradural block. Reduction in expired minute volume was observed in the two groups. Pa_{CO_2} and alveolar–arterial oxygen tension difference increased, and Pa_{O_2} decreased significantly 25 min after both blocks. These results demonstrate that pulmonary ventilation is slightly impaired by the two blocks and to the same degree, but ventilatory reserve and capacity are markedly impaired by cervical extradural block.

The use of cervical extradural analgesia for surgery of the neck, chest and upper limb has been reported (Fujikawa et al., 1948; Crawford et al., 1951; Bonica et al., 1957; Crawford, Brasher and Buckingham, 1957; Kosaka et al., 1978). Although Bromage (1978) has reported that intensity of motor block with plain lignocaine is negligible regardless of the concentration, this block may reduce respiratory function by intercostal and phrenic nerve paralysis, especially after injection of a high concentration of local anaesthetic agent such as 2% mepivacaine.

The present study was designed to estimate the degree of ventilatory impairment following cervical extradural analgesia, and to determine whether the ventilatory impairment following cervical block was more pronounced than that following thoracic block.

METHODS

Subjects

Thirty women patients aged 35–59 yr, were studied before surgery. They had no cardiovascular or respiratory abnormality as assessed by physical examination, chest x-ray and pulmonary function tests, in which the vital capacity (VC) was more than 80% of predicted value and the forced expiratory volume in one second (FEV_1) was more than 70% of the forced vital capacity (FVC). They were assigned to two groups of 15: group 1 received cervical extradural block to undergo breast surgery; group 2 received thoracic extradural block to undergo gallbladder surgery. Mean and SEM of age, height and weight in the two groups are shown in table I. The nature and extent of the investigation had been explained to the subjects and their informed consent was obtained.

Extradural analgesia

No premedication was given. About 200 ml of Ringer-lactate solution was administered by i.v. infusion during the course of the study in group 1 to ensure access to a vein. In group 2, 300–500 ml of hydroxyethyl starch solution was administered to avoid hypotension during extradural analgesia.

Each patient was placed in the lateral position to perform extradural block. The C7–T1 interspace in group 1 or the T12–L1 interspace in group 2 was identified, and an 18-gauge Tuohy needle was inserted by midline approach into the extradural space which was identified by the hanging-drop technique. Extradural analgesia was produced by injection of 2% mepivacaine 10 ml without adrenaline. The solution was injected as a single dose at a rate of 0.5 ml s^{-1}. A test dose was not used. A catheter was inserted cranially to a distance of 5 cm after injection of mepivacaine.

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0007-0912/80/121271-06 $01.00

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TABLE I. *Details of patients studied (mean ± SEM)*

Group	Number of patients	Age (yr)	Height (cm)	Weight (kg)
1: Cervical block	15	47.0 ± 1.7	152.8 ± 0.8	57.3 ± 1.9
2: Thoracic block	15	48.2 ± 2.0	153.6 ± 1.6	59.4 ± 2.8

Following removal of the needle, the patient was moved into the supine position. Analgesia was produced to an average level of C4, extending to T7 in group 1, and T5–L4 in group 2, as assessed by pin-prick test 20 min after injection.

Arterial pressure was measured with a sphygmomanometer. The decreases in systolic arterial pressure were less than 10 mm Hg during the course of the study in all patients in group 1. In group 2, systolic arterial pressure was maintained greater than 100 mm Hg in all patients, ephedrine being administered i.v. to six patients.

Measurements

Lung volumes, expired gas volumes, respiratory frequency (*f*), FEV_1, FEV_1/FVC ratio and maximum mid-expiratory flow rate (MMF) were recorded for all patients on the day before operation. The measurements were repeated 30 min after extradural injection. All measurements were made with the patients in a supine position to avoid postural hypotension during extradural analgesia. Functional residual capacity (FRC) was measured by the closed-circuit helium-dilution technique, using a Godart FRC computer. A Godart spirometer (Expirograph 16000), mouthpiece and noseclip were used to determine the other subdivisions of total lung capacity (TLC) and expired minute volume ($\dot{V}_E$), and to perform the dynamic tests of ventilatory capacity. Tidal volume (V_T) was derived from the measured values of $\dot{V}_E$ and respiratory frequency. The measured values were corrected to BTPS.

Arterial blood was taken from a femoral artery by direct puncture into heparinized glass syringes. Arterial puncture was made with a 23-gauge needle without the use of local anaesthesia. Samples were taken before all procedures and 25 min after extradural injection. Immediately after sampling, Pa_{O_2} and Pa_{CO_2} were determined using a Radiometer ABL1 blood-gas analyser. The results were not corrected for body temperature. Alveolar–arterial oxygen tension difference ($PA_{O_2} - Pa_{O_2}$) was calculated by applying the following formula:

$$(PA_{O_2} - Pa_{O_2}) = (PI_{O_2} - Pa_{CO_2}/R) - Pa_{O_2},$$

where PI_{O_2} is the inspired oxygen tension and was taken to be 19.86 kPa; R is the respiratory exchange ratio and a value of 0.8 was assumed.

Data were analysed using Student's *t* test for paired data within the two groups and for unpaired data between the two groups. Statistical significance was assumed when *P* values were 0.05 or less.

Anaesthesia during surgery

After all investigations had been performed, a further suitable dose of 1.5% mepivacaine with adrenaline was administered through the extradural catheter and surgery was performed. Diazepam 5–10 mg was given intermittently for sedation. Two patients in group 2 required anaesthesia during surgery when nitrous oxide, oxygen and a low concentration of halothane were administered following endotracheal intubation.

RESULTS

The spirometric and blood-gas data are shown in table II. There were no significant differences between the two groups with respect to age and body build (table I) or the spirometric and blood-gas values before extradural block (table II).

Lung volumes

During extradural analgesia, inspiratory capacity (IC), VC and TLC decreased significantly in the two groups ($P < 0.01$). Mean IC decreased by 28% in group 1 and 11% in group 2. Mean VC decreased by 25% in group 1 and 13% in group 2. Mean TLC decreased by 17% in group 1 and 9% in group 2. These changes were greater in group 1 than in group 2 ($P < 0.05$). Expiratory reserve volume (ERV) and FRC did not change in group 1, but in group 2 mean ERV decreased by 25% ($P < 0.01$) and mean FRC decreased by 6% during extradural analgesia ($P < 0.05$). Residual volume (RV) did not change in either group. An increase in

TABLE II. *Lung volumes, ventilation values, dynamic tests of ventilatory capacity and blood-gas tensions before and during extradural analgesia.* * *Significantly greater* ($P<0.05$) *compared with mean percentage alteration of group 2; n.s. = not significant*

	Group 1. cervical				Group 2: thoracic			
	Before extradural (mean ± SEM)	During extradural (mean ± SEM	Mean percentage alteration	*P*	Before extradural (mean ± SEM)	During extradural (mean ± SEM)	Mean percentage alteration	*P*
IC (litre)	2.35 ± 0.07	1.70 ± 0.11	−28*	<0.01	2.41 ± 0.10	2.14 ± 0.10	−11	<0.01
ERV (litre)	0.48 ± 0.04	0.42 ± 0.03	−12	n.s.	0.38 ± 0.04	0.29 ± 0.03	−25	<0.01
VC (litre)	2.81 ± 0.08	2.12 ± 0.14	−25*	<0.01	2.79 ± 0.11	2.43 ± 0.11	−13	<0.01
RV (litre)	1.26 ± 0.06	1.29 ± 0.10	+3	n.s.	1.22 ± 0.06	1.22 ± 0.06	0	n.s.
FRC (litre)	1.73 ± 0.08	1.71 ± 0.12	−1	n.s.	1.60 ± 0.08	1.51 ± 0.06	−6	<0.05
TLC (litre)	4.10 ± 0.10	3.40 ± 0.19	−17*	<0.01	3.99 ± 0.13	3.64 ± 0.14	−9	<0.01
RV/TLC (%)	30.5 ± 1.2	38.0 ± 2.2	+25*	<0.01	30.7 ± 1.2	33.8 ± 1.3	+10	<0.01
V_T (litre)	0.44 ± 0.02	0.35 ± 0.02	−21	<0.01	0.46 ± 0.02	0.37 ± 0.01	20	<0.01
f (b.p.m.)	17.2 ± 0.9	16.4 ± 0.8	−5	n.s	14.9 ± 0.7	14.7 ± 0.8	−1	n.s.
$\dot{V}_E$ (litre min^{-1})	7.44 ± 0.38	5.55 ± 0.20	−25	<0.01	6.78 ± 0.34	5.37 ± 0.26	−21	<0.01
FEV_1 (litre)	2.10 ± 0.08	1.59 ± 0.11	−25*	<0.01	2.16 ± 0.11	1.89 ± 0.10	−12	<0.01
FEV_1/FVC (%)	76.6 ± 2.1	76.8 ± 3.4	0	n.s.	80.5 ± 1.8	78.8 ± 2.1	−2	n.s.
MMF (litre min^{-1})	2.12 ± 0.18	1.64 ± 0.18	−23	<0.05	2.36 ± 0.22	1.94 ± 0.19	−18	<0.05
Pa_{O_2} (kPa)	11.56 ± 0.37	10.52 ± 0.37	−9	<0.01	11.51 ± 0.32	10.80 ± 0.30	−6	<0.01
Pa_{CO_2} (kPa)	4.84 ± 0.08	5.00 ± 0.09	+3	<0.05	4.80 ± 0.11	4.96 ± 0.13	+3	<0.05
$(PA_{O_2} - Pa_{O_2}$ (kPa)	2.25 ± 0.40	3.11 ± 0.41	+38	<0.01	2.36 ± 0.33	2.87 ± 0.29	+22	<0.01

the RV/TLC ratio was seen in both groups ($P<0.01$).

Ventilation

Thirty min after extradural block, mean $\dot{V}_E$ decreased by 25% in group 1 ($P<0.01$) and 21% in group 2 ($P<0.01$). These changes resulted from reductions of V_T because respiratory frequency did not change in either group. Mean V_T decreased by 21% in group 1 ($P<0.01$) and 20% in group 2 ($P<0.01$). The differences in $\dot{V}_E$ and V_T between the two groups were not significant.

Dynamic tests of ventilatory capacity

During extradural analgesia, mean FEV_1 decreased by 25% in group 1 ($P<0.01$) and 12% in group 2 ($P<0.01$). The change in FEV_1 was greater in group 1 than in group 2 ($P<0.05$). However, there was no change in FEV_1/FVC in either group, because of the same degree of reductions of FEV_1 and FVC. Mean MMF also decreased in the two groups after extradural block, in group 1 by 23% ($P<0.05$), in group 2 by 18% ($P<0.05$), but there was no significant difference between the two groups.

Arterial blood-gas tensions

Pa_{CO_2} increased significantly during extradural analgesia. The mean increase in each group was 0.16 kPa ($P<0.05$). Extradural analgesia was associated with a decrease in Pa_{O_2} of 1.04 kPa in group 1 ($P<0.01$) and 0.71 kPa in group 2 ($P<0.01$). ($PA_{O_2}-Pa_{O_2}$) increased in the two groups; in group 1 by 38% ($P<0.01$), in group 2 by 22% ($P<0.01$). The differences in Pa_{O_2} and ($PA_{O_2}-Pa_{O_2}$) between the two groups were not significant.

DISCUSSION

The present study shows that the impairment of resting ventilation following cervical extradural block is similar to that following thoracic extradural analgesia in conscious subjects. However, the impairment of carbon dioxide elimination and arterial oxygenation does not preclude the use of these blocks. The mean increase in Pa_{CO_2} of 0.16 kPa in both groups was very small and all values remained within the normal range. Although reduction in Pa_{O_2} was also observed in both groups, Pa_{O_2} could be maintained greater than 13 kPa by administering oxygen.

The reductions in IC, VC, TLC, and FEV_1 were greater in group 1 than in group 2, although the reduction of MMF was not. The reductions in ventilatory reserve and capacity show that extradural analgesia diminishes the ability to cough and to remove bronchial secretion. The decreased ability to cough is of no concern during surgery, but when extradural analgesia is used for the relief of pain after operation, it is necessary to use a concentration of local anaesthetic less than 2% mepivacaine. We use 1% mepivacaine for analgesia after operation, since it produces less effects on ventilatory reserve and capacity (Takasaki et al., 1978) but the analgesia produced is not adequate for extensive surgical manipulation.

Inspiratory capacity, VC and TLC were decreased in group 1. The decreases of VC and TLC were caused by the change in IC, since there were no changes in ERV and FRC. However in group 2, reductions in ERV and FRC were present in addition to relatively small reductions in IC, VC, and TLC.

The effect of cervical extradural analgesia on respiratory function has not been reported previously. However, there are a few clinical reports about some aspects of respiratory function following thoracic extradural analgesia. Moir and Mone (1964), Sjögren and Wright (1972) and McCarthy (1976) have shown that high extradural block to the level of the upper thoracic segments produced insignificant changes in pulmonary ventilation and blood-gas tensions, but Moir (1963) showed that a high extradural block to between T2 and T5 using 1.5% lignocaine produced a significant reduction (78 ml or 1%) of $\dot{V}_E$. Drummond and Littlewood (1977) found a trend of decreasing Pa_{O_2} during extradural block. In this study we found a significant reduction of $\dot{V}_E$ and impairment of pulmonary gas exchange. Although the increase in Pa_{CO_2} and decrease in Pa_{O_2} are statistically significant in our study, it is doubtful if the magnitude of these changes is clinically significant. There have been studies in which FRC has been unchanged by the induction of thoracic extradural analgesia (Wahba et al., 1972; McCarthy, 1976). However, ERV was reduced significantly in this and other studies (Freund et al., 1967) because of partial paralysis of lower thoracic and abdominal muscles. A significant reduction of FRC in this study was attributed to a reduction in ERV because RV would be unaffected by weakness of expiratory muscles. Dynamic tests of ventilatory capacity such as peak expiratory flow, FVC and FEV_1 were also decreased significantly in other studies (5–9%) (Moir, 1963; Sjögren and Wright, 1972). These changes are slightly less than those found in the present study but the differences could have resulted from differences in the sex of subjects. In this study all patients were female.

Freund and others (1967) observed that the level of motor blockade was 4.6 segments lower than the level of sensory blockade. The level of motor block would then have been at T9.6 in our study because the mean level of cutaneous analgesia was T5 in group 2. Inspiration is performed by the action of the diaphragm and the 5th–9th external intercostal muscles (Campbell, 1955), so the muscular activity of inspiration should not have been impaired in group 2. However, in this study a decrease in IC and an increase in ($PA_{O_2} - Pa_{O_2}$) were observed. From this evidence we believe that incomplete motor block to the 5th thoracic nerve was present in group 2. For the same reason, we believe that diminished mobility of the diaphragm and chest wall was present in group 1. The reduction of ventilatory capacity found would result from weakness of the expiratory muscles.

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FONCTION RESPIRATOIRE AU COURS D'ANALGESIE EXTRADURALE CERVICALE ET THORACIQUE CHEZ DES PATIENTS AUX POUMONS NORMAUX

RESUME

On a mesuré les volumes pulmonaires, les volumes de gaz expirés, les essais de capacité ventilatoire et les pressions gaz-sang chez des femmes soumises à une analgésie extradurale cervicale ou thoracique induite au moyen de mépivacaine à 2%. La capacité inspiratoire, la capacité vitale et la capacité pulmonaire ainsi que le FEV_1 diminuèrent tous de façon significative 30 min après l'induction des blocages extraduraux tant cervicaux que thoraciques. Les modifications observées au cours du blocage cervical furent beaucoup plus importantes que celles notées au cours de l'analgésie extradurale thoracique. Le volume de réserve expiratoire et la capacité fonctionnelle résiduelle baissèrent de manière significative après le blocage extradural thoracique, mais ne varierent pas après le blocage extradural cervical. On observa une réduction du volume-minute expiré chez les deux groupes. La différence de pression artérielle–alvéolaire d'oxygène et le Pa_{CO_2} augmentèrent, tandis que le Pa_{O_2} baissa de manière significative 25 min après chacun des blocages. Ces résultats démontrent que la ventilation pulmonaire est légèrement affectée par les deux blocages dans la même mesure alors que la capacité et la réserve ventilatoires souffrent grandement du blocage extradural cervical.

DIE ATMUNGSFUNKTION WÄHREND EXTRADURALER ANALGESIE IM ZERVIKAL- UND BRUSTRAUM BEI PATIENTEN MIT NORMALEN LUNGEN

ZUSAMMENFASSUNG

Lungenvolumen, ausgeatmete Gasvolumen, Untersuchungen des Luftfassungsvermögens und der Blutgasdrücke wurden vor und nach Einleitung einer extraduralen Analgesie im Zervikal- oder Brustraum mittels 2% Mepivacaine bei Frauen gemessen. Inspirationskapazität, Vitalkapazitat, Gesamtlungenkapazität und FEV_1 wurden alle 30 Minuten nach extraduraler Blockade im Zervikalraum und im Brustraum bedeutend vermindert. Die bei der Zervikalblockade beobachteten Änderungen waren bedeutend grösser als die Änderungen während der extraduralen Analgesie des Brustraums. Expiratorisches Reservevolumen und funktionelle Residualkapazität nahmen

nach der extraduralen Brustraumblockade bedeutend ab, änderten sich aber nach extraduraler Zervikalblockade nicht. Eine Verminderung des expiratorischen Minutenvolumens wurde bei beiden Grupen festgestellt. Pa_{CO_2} und alveolär-arterielle Sauerstoffdruckdifferenzen nahmen zu und Pa_{O_2} nahm 25 Minuten nach beiden Blockaden bedeutend ab. Diese Ergebnisse zeigen, dass die Lungendurchlüftung durch die zwei Blockaden geringfugig und im gleichen Masse beeinträchtigt wird, aber dass Reservevolumen und Kapazität durch extradurale Blockade im Zervikalraum bedeutend beeinträchtigt werden.

FUNCION RESPIRATORIA DURANTE LA ANALGESIA EXTRADURAL DE LA CERVIZ Y DEL TORAX EN PACIENTES CON PULMONES NORMALES

SUMARIO

Se midieron los volúmenes pulmonares, los volúmenes de gas expirado y se efectuaron pruebas de la capacidad de ventilación y de la tensión gaseosa en la sangre en mujeres, antes y después de la inducción de analgesia extradural de la cerviz y del tórax, usando mepivacaina al 2%. La capacidad de inspiración, la capacidad total, la capacidad pulmonar total y el FEV_1 disminuyeron todos ellos de forma significativa después de transcurridos 30 min de los bloqueos extradurales del cerviz y del tórax. Los cambios observados durante el bloqueo de la cerviz fueron significativamente superiores a los observados durante la analgesia extradural del tórax. El volumen espiratorio de reserva y la capacidad residual funcional disminuyeron significativamente después del bloqueo extradural del tórax, pero no variaron después del bloqueo extradural de la cerviz. En ambos groupos se apreció una reducción del volumen espirado. La Pa_{CO_2} y la diferencia de la tensión de oxigeno alveolar-arterial incrementó y la Pa_{O_2} disminuyó de forma significativa 25 min después de ambos bloqueos. Estos resultados demuestran que la ventilación pulmonar queda ligeramente impedida por los dos bloqueos, y al mismo nivel, pero la reserva y capacidad de ventilación quedan notablemente impedidas por el bloqueo extradural del cerviz.

Br. J. Anaesth. (1980), 52, 1277

THIOPENTONE–NITROUS OXIDE–HALOTHANE ANAESTHESIA AND SUXAMETHONIUM: PRETREATMENT WITH PANCURONIUM AND GALLAMINE

B. C. JØRGENSEN, B. EIKARD, J. P. RASMUSSEN AND J. VIBY-MOGENSEN

SUMMARY

Eighty healthy adult patients randomly allocated to four groups received pancuronium 0.01, 0.015, 0.02 mg kg^{-1} or gallamine 0.3 mg kg^{-1} i.v. 3 min before induction. Just before induction of anaesthesia, the patients were examined for signs and symptoms of neuromuscular blockade. After induction of anaesthesia with thiopentone, suxamethonium 1.5 mg kg^{-1} was administered i.v. Five minutes later the second dose was injected. No serious arrhythmia was seen in any of the four groups following the repeated dose of suxamethonium. However, the highest dose of pancuronium (0.02 mg kg^{-1}) caused an unacceptably high frequency of partial neuromuscular blockade.

It has been shown that preanaesthetic administration of gallamine 0.3 mg kg^{-1} affords protection against severe arrhythmia following repeated doses of suxamethonium in patients anaesthetized with halothane and nitrous oxide after induction with thiopentone (Viby-Mogensen, Wisborg and Sørensen, 1980).

Pancuronium has never been investigated in this respect during halothane anaesthesia. We have compared the protective effect of different doses of pancuronium and gallamine against severe arrhythmia following a second dose of suxamethonium during thiopentone–nitrous oxide–oxygen–halothane anaesthesia, and have attempted to determine the dose of pancuronium which causes the same low frequency of side-effects as gallamine 0.3 mg kg^{-1}

MATERIALS AND METHODS

Patients

Eighty healthy patients who underwent minor surgical procedures gave informed consent for the study. They were randomly allocated to four groups (table I).

Anaesthesia

Figure 1 shows the anaesthetic procedure. Diazepam 0.1 mg kg^{-1} was given i.m. 60 min before induction.

Three minutes before induction, pancuronium or gallamine was administered i.v. according to the group to which they had been allocated. Anaesthesia was induced by injection of thiopentone 4–5 mg kg^{-1} i.v. Ventilation of the lungs was controlled throughout the study to keep Pa_{CO_2} constant. Anaesthesia was maintained with 50% nitrous oxide in oxygen with halothane 1% using a semi-closed circle system with carbon dioxide absorption.

One minute after induction, and exactly 5 min later, suxamethonium 1.5 mg kg^{-1} was given i.v. The trachea was not intubated and no patient received surgery during the observation period.

Measurements

Before injection of pancuronium or gallamine and before induction of anaesthesia, the patients were questioned and examined for symptoms and signs of partial neuromuscular blockade.

E.c.g. lead II was monitored continuously throughout the procedure. The heart rate was determined from the e.c.g.

Blood samples were drawn for measurements of serum potassium concentration, Pa_{CO_2} and Pa_{O_2} before anaesthesia and 3 min after injection of suxamethonium.

Serum potassium was measured with the flame photometric method and blood-gas tensions were measured with a Radiometer ABL 1 acid–base machine. Arterial pressure was recorded non-invasively every 5 min.

To exclude changes in cardiac rate and rhythm

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0007–0912/80/121277–05 $01.00

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TABLE I. *Doses of pancuronium or gallamine administered i.v. 3 min before induction, number of patients, sex and age distribution in each of the four groups*

Group	Drug	No. of patients	Male	Mean age (yr) (range)
I	Pancuronium 0.01 mg kg^{-1}	20	12	38.8 (25–54)
II	Pancuronium 0.015 mg kg^{-1}	20	12	41.5 (19–63)
III	Pancuronium 0.02 mg kg^{-1}	20	11	37.7 (18–61)
IV	Gallamine 0.3 mg kg^{-1}	20	13	37.1 (24–60)
I+II+III+IV		80	48	38.8 (18–63)

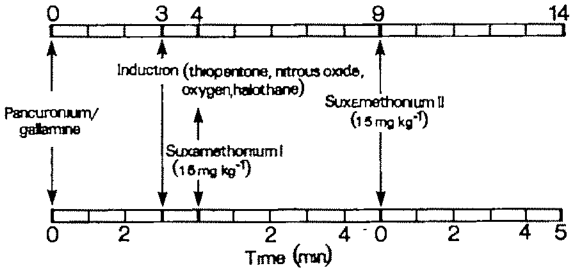
0
3
4
9
14
Induction (thiopentone, nitrous oxide, oxygen, halothane)
Pancuronium/ gallamine
Suxamethonium II (1.5 mg kg⁻¹)
Suxamethonium I (1.5 mg kg⁻¹)
0
2
2
4
0
2
4
5
Time (min)

FIG. 1. Time sequence of anaesthesia and administration of drugs.

caused by gross alterations in Pa_{CO_2}, the results include only those patients in whom the Pa_{CO_2} was between 3.3 and 6.7 kPa (25 and 50 mm Hg) throughout the procedure.

The statistical analysis were performed using the Chi-square test, Fisher exact probability test, Kruskal–Wallis test and Wilcoxon matched-pairs signed-ranks test. Significance was assigned at a level of 0.05.

RESULTS

Cardiac rate and rhythm

Preinduction period. The heart rates throughout the study are shown in figure 2.

There were no significant ($P > 0.05$) differences between the control values of the four groups. After injection of pancuronium or gallamine, the heart rate increased in groups II, III, and IV ($P < 0.05$), but not in group I.

Induction and first injection of suxamethonium. After the injection of thiopentone there was a

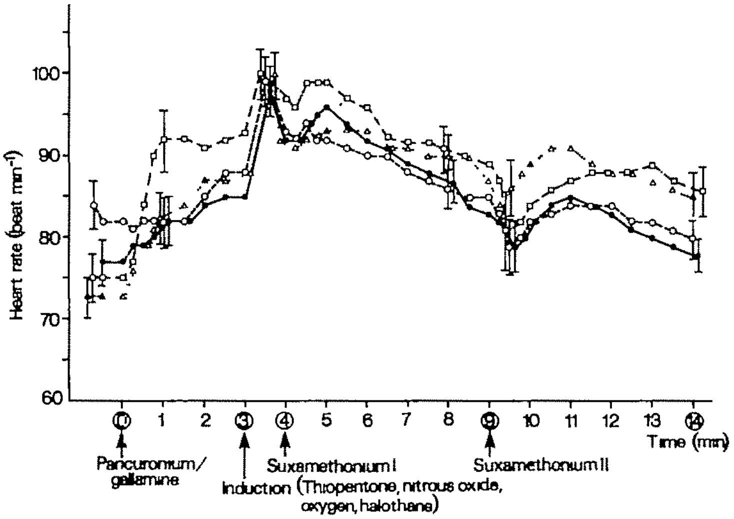

FIG. 2. Heart rates during the observation period. Mean values ±SEM are are shown. Group I (pancuronium 0.01 mg kg^{-1}) = ○- -○; Group II (pancuronium 0.015 mg kg^{-1}) = ●——●; Group III (pancuronium 0.02 mg kg^{-1}) = △...△; Group IV (gallamine 0.3 mg kg^{-1}) = □–□.

significant increase ($P<0.05$) in heart rate in groups I, II, and III. This was in contrast to the gallamine group in whom only a slight and insignificant increase in heart rate was found.

Only minor and insignificant changes in heart rate were seen following the first injection of suxamethonium.

Second injection of suxamethonium (fig. 2). The mean heart rate decreased in all groups after the second injection of suxamethonium, although not significantly. The lowest rates occured 15 s after the injection in group III and 30 s after in group I, II, and IV, but no significant differences between the heart rates in the four groups were observed within the first 30 s after the second injection of suxamethonium.

Figure 3 shows the changes in heart rate and rhythm for each patient during the first 45 s after the second injection of suxamethonium and the number of patients exhibiting arrhythmia. Bradycardia (heart rate less than 60 beat min^{-1}) was seen in two (group I), two (group II), one (group III), and three (group IV) patients. There were no significant differences between the groups. Heart rates less than 40 beat min^{-1} were seen in no, one, one, and two patients, respectively.

Severe bradycardia (heart rate less than 20 beat min^{-1}) and tachycardia (heart rate greater than 120 beat min^{-1}) did not occur in any of the patients. One of the patients in group IV had an episode of total A–V dissociation lasting 45 s; after this sinus rhythm reappeared spontaneously.

Signs and symptoms following pancuronium or gallamine (table II)

Three minutes after administration of pancuronium or gallamine i.v. a sensation of heavy

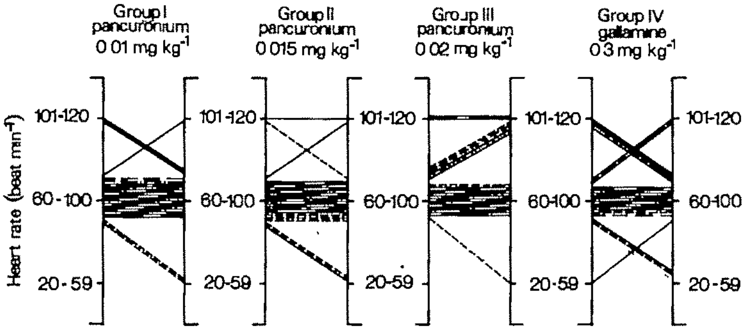

FIG. 3. Changes in heart rate over the first 45 s after the second injection of suxamethonium. Each line represents one patient. — — — = Nodal rhythm or nodal extrasystoles; -·-·- = ventricular extrasystoles; ······ = A–V dissociation.

TABLE II. *Symptoms and signs 3 min after i.v. administration of pancuronium or gallamine. * Significant difference between the groups* (P<0.05)

	Group			
	I	II	III	IV
	Pancuronium 0.01 mg kg^{-1}	Pancuronium 0.015 mg kg^{-1}	Pancuronium 0.02 mg kg^{-1}	Gallamine 0.3 mg kg^{-1}
No. of patients	20	20	20	20
Symptoms				
Heavy eye-lids	17	20	20	20
Blurring of vision	15	17	20	16
Sleepiness	11	12	13	11
Difficulty in breathing *	0	0	5	0
General discomfort *	1	5	10	2
Signs				
Ptosis *	14	19	20	17
Difficulties in lifting head *	3	2	10	2
Difficulties in breathing *	1	0	5	1

eye-lids, blurring of vision and sleepiness occurred in most of the patients in all groups.

The frequency of general discomfort, difficulty in breathing and in lifting the head was significantly greater in group III than in the other groups. The frequency of ptosis was significantly less in group I than in the other groups.

Pa_{CO_2}, Pa_{O_2} and serum potassium

Only minor variations occurred, and no significant differences were found between the groups.

Arterial pressure

The changes in arterial pressure were small and in no case was the systolic arterial pressure less than 11.3 kPa (85 mm Hg).

DISCUSSION

Our results indicate that preinduction administration of pancuronium is as effective as gallamine in protecting against severe arrhythmia following a second dose of suxamethonium during thiopentone–nitrous oxide–oxygen–halothane anaesthesia. Mathias, Evans-Prosser and Churchill-Davidson (1970) proposed the use of pancuronium 0.03 mg kg^{-1} to prevent the occurrence of severe arrhythmia after a second dose of suxamethonium. However, their patients differed from ours in that they did not receive halothane, and the second injection of suxamethonium was not given exactly 5 min after the first, but when spontaneous breathing had returned. Mathias' patients were not studied for signs or symptoms of partial neuromuscular blockade. Our study clearly shows that the largest dose of pancuronium (0.02 mg kg^{-1}) caused a high frequency of clinical signs and symptoms of partial neuromuscular blockade, indicating that pancuronium 0.03 mg kg^{-1} would be unacceptable.

We conclude that, in adult patients, preanaesthetic administration of pancuronium 0.01 and 0.015 mg kg^{-1} i.v. will be as effective as gallamine 0.3 mg kg^{-1} in protecting against severe arrhythmia following a second dose of suxamethonium during thiopentone–nitrous oxide–halothane anaesthesia with the same low frequency of side-effects. Increasing the dose of pancuronium to 0.02 mg kg^{-1} causes an unacceptably high frequency of side-effects.

ACKNOWLEDGEMENTS

We would like to thank the nurses in the anaesthetic department and the operating theatres and our surgical colleagues for their patience and helpfulness. We acknowledge with appreciation the assistance provided by our laboratory staff.

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ANESTHESIE PAR THIOPENTONE-OXYDE NITREUX-HALOTHANE ET SUXAMETHONIUM: TRAITEMENT PREALABLE AU PANCURONIUM ET GALLAMINE

RESUME

On a réparti au hasard quatre-vingts patients adultes en bonne santé en quatre groupes auxquels on administra 0,01, 0,015, 0,02 mg kg^{-1} de pancuronium i.v. ou 0,3 mg kg^{-1} de gallamine i.v. 3 min avant l'induction. Immédiatement avant l'induction de l'anesthésie, on examina les patients afin de découvrir les signes et symptômes de blocage neuromusculaire. Après l'induction de l'anesthésie au thiopentone, on administra 1,5 mg kg^{-1} de suxaméthonium i.v. Cinq minutes plus tard, on leur administra une deuxième dose. Aucune arrythmie grave ne s'est produite dans l'un quelconque des quatre groupes à la suite de la deuxième dose de suxaméthonium. Toutefois, la dose la plus forte de pancuronium (0,02 mg kg^{-1}) provoqua une apparition de blocage neuromusculaire partiel beaucoup trop fréquent pour être acceptable.

THIOPENTON-STICKSTOFFOXYDUL-HALOTHAN-ANÄSTHESIE UND SUXAMETHONIUM: VORBEHANDLUNG MIT PANCURONIUM UND GALLAMIN

ZUSAMMENFASSUNG

Achtzig gesunde erwachsene Patienten wurden willkürlich in 4 Gruppen aufgeteilt und bekamen Pancuronium 0,01, 0,015, 0,02 mg kg^{-1} bzw. Gallamin 0,3 mg kg^{-1} 3 Minuten vor Einleitung des Anästhesie intravenös verabreicht. Kurz vor der Einleitung der Anästhesie wurden die Patienten auf Anzeichen oder Symptome von neuromuskulärer Blockade untersucht. Nach Einleitung der Anästhesie durch Thiopenton wurde Suxamethonium 1.5 mg kg^{-1} intravenös verabreicht. Fünf Minuten später wurde die zweite Dosis injiziert. Nach der wiederholten Dosierung mit Suxamethonium wurde bei keiner der vier Gruppen eine ernsthafte Arrhythmie beobachtet. Die grösste Dosis von Pancuronium (0,02 mg kg^{-1}) verursachte jedoch eine unannehmbar hohe Frequenz von partieller neuromuskulärer Blockade.

ANESTESIA MEDIANTE SUXAMETONIUM Y TIOPENTONA-OXIDO NITROSO-HALOTANO: PRETRATAMIENTO CON PANCURONIUM Y GALLAMINA

SUMARIO

Antes de efectuar la inducción se administraron 0,01, 0,015 y 0,02 mg kg^{-1} de pancuronium o 0,3 mg kg^{-1} de gallamina a 80

pacientes adultos y sanos que se asignaron de forma aleatoria en cuatro grupos. Justo antes de inducir la anestesia, se examinó a los pacientes en busca de signos y síntomas de bloqueo neuromuscular. Después de inducir la anestesia con tiopentona, se administraron 1,5 mg kg^{-1} de suxametonium por vía intravenosa. La segunda dosis se administro cinco minutos después. No se observó arritmia seria en ninguno de los cuatro grupos después de la repetida dosis de suxametonium. No obstante, la dosis más alta de pancuronium (0,02 mg kg^{-1}) ocasionó, con frecuencia inaceptable, bloqueo neuromuscular parcial.

Br. J. Anaesth. (1980), 52, 1283

OBSTETRIC ANAESTHESIA AND EHLERS–DANLOS SYNDROME

E. ABOULEISH

SUMMARY

The obstetric and anaesthetic problems of Ehlers–Danlos syndrome are discussed. A new unclassified type of the syndrome is described. The possibility of bleeding presents a serious challenge for both the obstetrician and the anaesthetist. A detailed medical history, including family history, are important in determining the method of anaesthesia since blood coagulation tests are usually normal. The anaesthetic management of two parturients with Ehlers–Danlos syndrome is illustrated. Caudal, extradural, and subarachnoid block techniques for labour and Caesarean section were used safely on three occasions in these two patients.

Ehlers–Danlos syndrome (EDS) as a complication in obstetric practice is rare (Smith, Powell and Essin, 1968; Beighton, 1969; Mukerji, 1975). Reports on anaesthesia and EDS are few (Woolley, Morgan, and Hays, 1967; Dolan, Sisko and Riley, 1980), but there is none regarding the anaesthetic management of the parturient with EDS.

Ehlers–Danlos syndrome is usually inherited as an autosomal dominant trait. It is not limited to one race; recently, a similar syndrome has been described in animals (Hegreberg et al., 1970). It is a connective tissue disorder characterized by a defect in collagen synthesis. Thus, EDS affects almost every system in the body. This may lead to hyperdistensibility of the skin (El-Aziz, El-Khashab and El-Ashmawi, 1971; Hollister, 1978), hypermobility of joints, spontaneous rupture of hollow organs, spontaneous pneumothorax (Smit, Alberts and Balk, 1978; Scully, Galdabini and McNeely, 1979), skeletal abnormalities (Zaidi, 1959), visual loss, peridontitis, and cardiovascular anomalies (Barabas, 1972; Bowers, Spencer and McDevitt, 1976; McKusick, 1978; Marquez et al., 1978; Wright et al., 1979).

Spontaneous postoperative or postpartum bleeding in patients with EDS can be life-threatening (Scully, Galdabini and McNeely, 1979; Dolan, Sisko and Riley, 1980). Laryngoscopy and tracheal intubation may lead to bleeding and encroachment on the upper airway. Extradural, subarachnoid or caudal block in such patients is contraindicated because a blood vessel may be damaged with the risks of haematoma formation.

The different manifestations of EDS usually occur in consistent patterns and degrees within families (McKusick, 1974).

CASE REPORT

During the past five years, of 36 257 parturients, two with a diagnosis of EDS were delivered at Magee-Womens Hospital.

Patient 1

A 31-yr-old White primigravida with EDS presented at 20 weeks gestation. Her grandfather, father, uncle, brother and two cousins suffered from the same type of EDS, which is still unclassified (fig. 1). Their syndrome is characterized by hypermobility of joints with a tendency to subluxation and dislocation, hypoplasia of the fourth metatarsal and fifth metacarpal bones, and an inclination to bleed from open wounds. Various members of the family as well as the patient had not bled following surgery if the wound had been closed and the tissues were approximated. At the age of 5 yr, the patient had received diethyl ether anaesthesia after which she suffered claustrophobia. and hypnophobia. Subsequent operations were performed under regional blocks or local infiltration anaesthesia. There was a history of pulmonary tuberculosis which had been treated successfully with chemotherapy.

Since our institution favours intravertebral nerve blocks, the patient was questioned particularly regarding such blocks. This revealed that

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0007–0912/80/121283–04 $01.00

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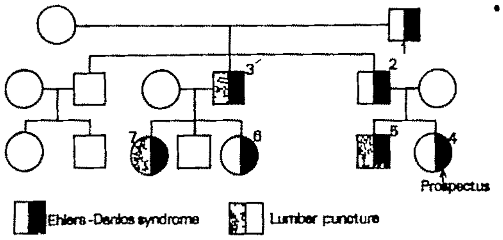

IG. 1. Patient 1—family pedigree. Affected members of the family: 1 = Grandfather (86-yr-old); 2 = father (60-yr-old); 3 = uncle (Spinal blocks at age 24 and 59 yr); 4 = prospectus; 5 = brother (two diagnostic lumbar punctures at age 5 yr; two spinal blocks at age 15 yr); 6 = cousin (20-yr-old had no anaesthesia or delivery); 7 = cousin (spinal blocks at ages 26, 27, and 28 yr for vaginal deliveries).

lumbar puncture for diagnostic or anaesthetic purposes had been performed without problems in some members of her family who suffered from the same syndrome (fig. 1). One of her cousins had three deliveries under subarachnoid block without anaesthetic or obstetric complications. The repeated blood coagulation tests of the patient performed in 1970, 1971, 1973, and 1974, were all normal.

On physical examination the patient was very anxious; pectus excavatum was noted and a functional systolic heart murmur was heard in the pulmonary area. The patient exhibited micrognathia, and a high-arched palate. The spinal curvature appeared normal with the caudal landmarks readily identifiable. Pulmonary function tests showed restrictive pulmonary disease (vital capacity 60% of predicted). The e.c.g. was normal. The haemoglobin concentration was 12.5 g dl^{-1} and the haematocrit was 37%. The blood group was B Rh-positive.

On September 7, 1974, the patient presented in active labour at 40 weeks gestation. Three litres of blood for transfusion were made available. Two i.m. injections of pethidine 50 mg were inadequate to control her labour pains. When the cervix was dilated 5 cm, continuous caudal analgesia was instituted. A 16-gauge Teflon cannula was used to pierce the posterior sacrococcygeal ligament (Abouleish, 1977). Once the ligament had been penetrated, the inner needle was withdrawn, and the soft cannula was advanced into the caudal canal. A 20-gauge Teflon catheter without a stylette was advanced through the caudal canal to minimize the dose of local anaesthetic used for labour and delivery, and to insure adequate anaesthesia for abdominal delivery if required. Bupivacaine 0.5% provided adequate analgesia for labour. However, Caesarean section was performed because of failure to progress and cephalopelvic disproportion. Twenty-five millilitre of 0.75% bupivacaine injected via the caudal cannula yielded effective anaesthesia for the abdominal delivery. The estimated blood loss during surgery was 650 ml. Both the operation and the postoperative course were unremarkable.

On April 8, 1977, the patient underwent a second elective Caesarean section at 39 weeks gestation. A single-injection extradural nerve block was achieved by injecting 0.75% bupivacaine 17 ml through a 17-gauge Tuohy needle at L3–4 space. Anaesthesia and surgery were uneventful.

Patient 2

A 19-yr-old White female underwent Caesarean section on July 27, 1977 because of prolonged rupture of membranes, failure to progress, and breech presentation. There had been a previous normal pregnancy and delivery in 1975. However, this pregnancy was complicated by hydramnios requiring prolonged hospitalization and antibiotic and corticosteroid therapy to promote fetal lung maturity. Repeated estimations of the lecithin–sphingomyelin ratio, shake tests, sonograms, and stress tests were performed to evaluate the fetal condition.

On examination, the patient was found to have a small frame and marked lordosis (140 cm tall; weight 50 kg). The sclerae were blue and there was distensibility of the skin, and "cigarette-paper" scars on the knees. Bone marrow biopsy and a fracture-free athletic past supported the diagnosis of EDS over a previous diagnosis of osteogenesis imperfecta. Neither the patient nor her family had a history of ecchymoses or excessive bleeding. Blood coagulation tests were normal.

For Caesarean section, subarachnoid block was induced using lignocaine 50 mg with adrenaline 0.2 mg injected at L3–4 space through a 26-gauge disposable spinal needle. The estimated blood loss during surgery was 600 ml. Both surgery and the postoperative course were uneventful.

DISCUSSION

In obstetric practice, EDS presents special problems. Miscarriages and prematurity occur commonly because of premature rupture of the membranes when the fetus is affected, and because of an incompetent cervical os when the mother is affected (Barabas, 1966; Smith, Powell and Essin, 1968; Beighton, 1969). During labour, separation of the symphysis pubis has been reported (Beighton, 1969) and postpartum, uterine prolapse may develop. In some patients haemorrhage during labour or postpartum can be fatal (Smith, Powell and Essin, 1968; Dolan, Sisko and Riley, 1980). Perineal haematoma and wound dehiscence may occur after delivery (Smith, Powell and Essin, 1968). Thus, episiotomy and Caesarean section are serious undertakings in a patient with EDS. An adequate supply of blood for transfusion should be available.

The cause of bleeding with EDS is unknown. Although there is an occasional platelet defect (Onel, Ulutin and Ulutin, 1973), the coagulation tests are usually normal (Hollister, 1978). The reduced ability of collagen to attract platelets contributes to the bleeding tendency (Karaca, Cronberg and Nilsson, 1972). The primary collagen defect increases the vascular fragility. The lack of tamponade and support of the surrounding connective tissue also plays a role (Rybka and O'Hara, 1967).

In the first case presented, the failure of two analgesic doses of pethidine prompted the choice of caudal block. Both the obstetrician and the anaesthetist considered that paracervical block would have been too risky for the fetus since the patient was having a slow and painful labour, and repeated blocks would have been needed. An intravertebral block seemed possible in view of her family history of safe lumbar punctures, her own history of previous regional block and surgery without bleeding, the absence of previous menorrhagia and ecchymoses, and the patient's tendency to bleed only from open wounds.

It was felt that a continuous caudal technique reduced the risk of vessel injury. A Teflon caudal cannula causes less trauma than an extradural needle. Also, the caudal catheter can advance in the direction of the cannula in the dorsal groove of the caudal canal while the extradural catheter, by making an almost 90° angle, enhances the chance of inadvertent vascular puncture.

On the second admission of this patient, her response to the continuous caudal block and the operative procedure of the first Caesarean section encouraged us to use extradural analgesia. A single-dose extradural technique would be expected to cause less vascular trauma than the continuous method. Because of the patient's restrictive pulmonary disease, extradural analgesia seemed preferable to spinal block. Claustrophobia and hypnophobia precluded general anaesthesia. Moreover, many problems could have been associated with general anaesthesia: micrognathia could have hindered tracheal intubation, positive pressure ventilation would have predisposed to pneumothorax because of EDS and previous tuberculous lesion.

The second patient and her family had no history of excessive bleeding. Therefore, the risk of aspiration pneumonitis was greater than the remote possibility of bleeding with spinal block. The premature rupture of membranes was suggestive of EDS in the baby. However, at the time of birth there was no evidence of the syndrome in the neonate, such as congenital dislocation of the hip or difficulty in tying the umbilical cord (Macfarlane, 1959; Beighton, 1969).

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ANESTHESIE EN OBSTETRIQUE ET SYNDROME D'EHLERS–DANLOS

RESUME

On discute des problèmes obstétriques et anesthétiques du syndrome d'Ehlers–Danlos. On décrit un nouveau type de syndrome non classé. La possibilité d'hémorragie présente un problème grave tant pour l'obstétricien que pour l'anesthésiste. Il est important de disposer de l'historique médicale détaillée, y compris l'historique familiale, pour déterminer la méthode d'anesthésie étant donné que les analyses de coagulation du sang sont en général normales. L'administration de l'anesthésie chez deux parturientes souffrant du syndrome d'Ehlers–Danlos est illustrée. A trois reprises, on utilisa chez ces deux patientes sans accident des techniques de blocage caudal, extradural et subarachnoide pour l'accouchement et la césarienne.

GEBURTSANÄSTHESIE UND EHLERS–DANLOS SYNDROM

ZUSAMMENFASSUNG

Die anästhesie- und geburtsbezogene Probleme des Ehlers–Danlos Syndroms werden diskutiert. Eine neue, bisher nicht eingeordnete Art des Syndroms wird beschrieben. Die Möglichkeit von Blutung stellt sowohl für Geburtshelfer als auch Anästhetisten ein ernsthaftes Problem dar. Eine detaillierte medizinische Vorgeschichte (inkl. Familiengeschichte) spielt bei der Bestimmung der zu verwenden Narkosemethode eine wichtige Rolle, da Blutgerinnbarkeitsproben gewöhnlich völlig normal verlaufen. Die Anästhetisierung von zwei Patientinnen mit Ehlers–Danlos-Syndrom wird erläutert. Kaudale, extradurale und subarachnoidale Blockierungsmethoden für Entbindungen und Kaiserschnitt wurden bei diesen zwei Patientinnen bei 3 verschiedenen Gelegenheiten erfolgreich verwendet.

SINDROME DE EHLERS–DANLOS Y ANESTESIA OBSTETRICA

SUMARIO

Se analizaron los problemas anestésicos y obstétricos relativos al síndrome de Ehlers–Danlos. Se describe un nuevo tipo de síndrome aún sin clasificar. La posibilidad de hemorragia presenta un serio problema tanto para el obstétrico como para el anestesista. El historial médico detallado es importante, incluyendo el historial familiar, a la hora de determinar el método anestésico a seguir, dado que las pruebas de coagulación de sangre son generalmente normales. Se ilustra la gerencia anestésica llevada a cabo en dos parturientas con el síndrome de Ehlers–Danlos. En estas dos pacientes se efectuaron en tres ocasiones y de forma segura técnicas de bloqueo de caudal, de bloqueo extradural y de bloqueo subaracnoideo para el parto y para el corte de cesárea.

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Printed in Great Britain by John Wright and Sons Ltd, at The Stonebridge Press, Bristol BS4 5NU

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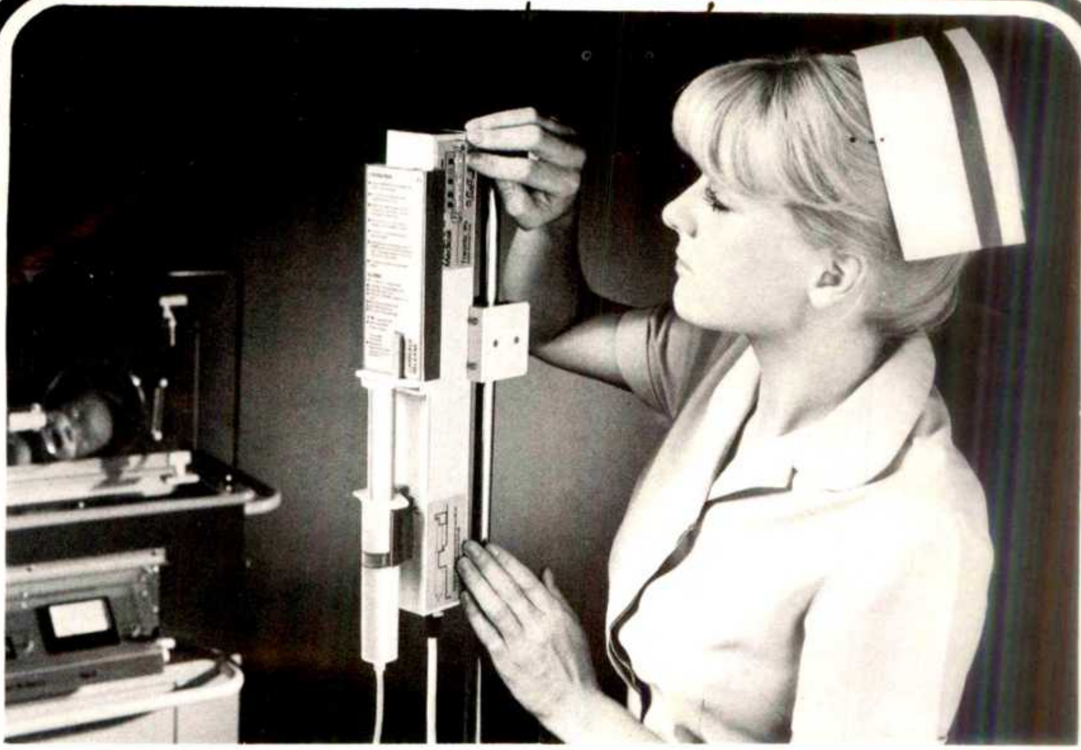

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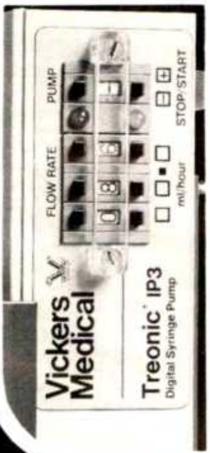

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 12 *Published monthly* DECEMBER 1980

Annual subscriptions (post free): U.K. £27.50; U.S.A. and Canada U.S.$65, Airmail U.S.$155; Rest of World £33.00, Airmail £65 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

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